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APPLICATION FOR UNITED STATES PATENT

MULTI-FUNCTIONAL HEMATOPOIETIC FUSION PROTEINS BETWEEN SEQUENCE REARRANGED G-CSF RECEPTOR AGONISTS AND OTHER HEMATOPOIETIC FACTORS

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CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application is a continuation of U.S. 09/510,238, filed February 22, 2002, Pat. App. Ser. No. 10 pending, which is a divisional of U.S. Pat. App. Ser. No. 08/835,162 filed April 4, 1997, now issued as U.S. Pat. No. 6,066,318 on May 23, 2000, which is a continuation-in-part of PCT/US 96/15774 filed October 4, 1996 which claims priority under 35 U.S.C. §119(e) of U.S. Provisional Pat. App. Ser. No. 15 60/004,834, filed October 5, 1995, now abandoned.

REFERENCE TO A "SEQUENTIAL LISTING," A TABLE, OR A COMPTUER PROGRAM LISTING APPENDIX SUBMITTED ON A DISKETTE

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[0002] This application includes a computer program listing appendix, pursuant to 37 CFR 1.96, contained on a diskette, which is incorporated fully into this application by this reference.

25 The diskette is labeled as follows:

> Applicant: Feng, et al.

Title: Multi-Functional Hematopoietic Fusion

> Proteins Between Sequence Rearranged G-CSF Receptor Agonists and Other Hematopoietic

Factors

Recorded: October 23, 2003

126181-1058 Atty No.:

Serial No.: Unknown

Filing Date: October 27, 2003

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The diskette contains the following file in ASCII file format:

File Name	File size	Creation Date	
Sequence.txt	574 kb	October 23, 2003	

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BACKGROUND OF THE INVENTION

[0003] The present invention relates to multi-functional hematopoietic receptor agonists.

10 [0004] Colony stimulating factors (CSFs) which stimulate the differentiation and/or proliferation of bone marrow cells have generated much interest because of their therapeutic potential for restoring depressed levels of hematopoietic stem cell-derived cells. CSFs in both human and murine systems 15 have been identified and distinguished according to their activities. For example, granulocyte-CSF (G-CSF) macrophage-CSF (M-CSF) stimulate the in vitro formation of neutrophilic granulocyte and macrophage colonies, respectively, while GM-CSF and interleukin-3 (IL-3) 20 broader activities and stimulate the formation of both macrophage, neutrophilic and eosinophilic granulocyte IL-3 also stimulates the formation of colonies. megakaryocyte and pure and mixed erythroid colonies.

25 DESCRIPTION OF RELATED ART

[0005] U.S. 4,877,729 and U.S. 4,959,455 disclose human IL-3 and gibbon IL-3 cDNAs and the protein sequences for which

they code. The hIL-3 disclosed has serine rather than proline at position 8 in the protein sequence.

[0006] International Patent Application (PCT) WO 88/00598 discloses gibbon- and human-like IL-3. The hIL-3 contains a Ser⁸ -> Pro⁸ replacement. Suggestions are made to replace Cys by Ser, thereby breaking the disulfide bridge, and to replace one or more amino acids at the glycosylation sites.

[0007] U.S. 4,810,643 discloses the DNA sequence encoding human G-CSF.

- 10 [0008] WO 91/02754 discloses a fusion protein comprised of GM-CSF and IL-3 which has increased biological activity compared to GM-CSF or IL-3 alone. Also disclosed are nonglycosylated IL-3 and GM-CSF analog proteins as components of the multi-functional hematopoietic receptor agonist.
- 15 [0009] WO 92/04455 discloses fusion proteins composed of IL-3 fused to a lymphokine selected from the group consisting of IL-3, IL-6, IL-7, IL-9, IL-11, EPO and G-CSF.
 - [0010] WO 95/21197 and WO 95/21254 disclose fusion proteins capable of broad multi-functional hematopoietic properties.
- 20 [0011] GB 2,285,446 relates to the c-mpl ligand (thrombopoietin) and various forms of thrombopoietin which are shown to influence the replication, differentiation and

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maturation of megakaryocytes and megakaryocytes progenitors which may be used for the treatment of thrombocytopenia.

[0012] EP 675,201 A1 relates to the c-mpl ligand (Megakaryocyte growth and development factor (MGDF), allelic variations of c-mpl ligand and c-mpl ligand attached to water soluble polymers such as polyethylene glycol.

[0013] WO 95/21920 provides the murine and human c-mpl ligand and polypeptide fragments thereof. The proteins are useful for *in vivo* and *ex vivo* therapy for stimulating platelet production.

REARRANGEMENT OF PROTEIN SEQUENCES

[0014] In evolution, rearrangements of DNA sequences serve an important role in generating a diversity of protein structure and function. Gene duplication and exon shuffling provide an important mechanism to rapidly generate diversity and thereby provide organisms with a competitive advantage, especially since the basal mutation rate is low (Doolittle, Protein Science 1:191-200, 1992).

[0015] The development of recombinant DNA methods has made it possible to study the effects of sequence transposition on protein folding, structure and function. The approach used in creating new sequences resembles that of naturally occurring pairs of proteins that are related by linear reorganization of

their amino acid sequences (Cunningham, et al., Proc. Natl. Acad. Sci. U.S.A. 76:3218-3222, 1979; Teather & Erfle, J. Bacteriol. 172: 3837-3841, 1990; Schimming et al., Eur. J. Biochem. 204: 13-19, 1992; Yamiuchi and Minamikawa, FEBS Lett. 260:127-130, 1991; MacGregor et al., FEBS Lett. 378:263-266). The first in vitro application of this type of rearrangement to proteins was described by Goldenberg and Creighton (J. Mol. Biol. 165:407-413, 1983). A new N-terminus is selected at an internal site (breakpoint) of the original sequence, the new sequence having the same order of amino acids as the original 10 from the breakpoint until it reaches an amino acid that is at near the original C-terminus. At this point the new sequence is joined, either directly or through an additional portion of sequence (linker), to an amino acid that is at or 15 near the original N-terminus, and the new sequence continues with the same sequence as the original until it reaches a point that is at or near the amino acid that was N-terminal to the breakpoint site of the original sequence, this residue forming the new C-terminus of the chain.

20 [0016] This approach has been applied to proteins which range in size from 58 to 462 amino acids (Goldenberg & Creighton, J. Mol. Biol. 165:407-413, 1983; Li & Coffino, Mol. Cell. Biol. 13:2377-2383, 1993). The proteins examined have represented a broad range of structural classes, including

proteins that contain predominantly a-helix (interleukin-4; et al., Cytokine 7:311-318, 1995), b-sheet Kreitman (interleukin-1; Horlick et al., Protein Eng. 5:427-431, 1992), or mixtures of the two (yeast phosphoribosyl anthranilate isomerase; Luger et al., Science 243:206-210, 1989). Broad categories of protein function are represented in these sequence reorganization studies:

		Enzymes
10	T4 lysozyme	<pre>Zhang et al., Biochemistry 32:12311-12318, 1993; Zhang et al., Nature Struct. Biol. 1:434-438 (1995).</pre>
15	dihydrofolate	Buchwalder et al., Biochemistry reductase 31 :1621-1630, 1994; Protasova et al., Prot. Eng. 7 :1373-1377, 1995).
20	ribonuclease T1	Mullins et al., J. Am. Chem. Soc. 116:5529-5533, 1994; Garrett et al., Protein Science 5:204-211, 1996).
	Bacillus b-glucanse	Hahn et al., <i>Proc. Natl. Acad. Sci.U.S.A.</i> 91 :10417-10421, 1994).
25	aspartate	Yang & Schachman, <i>Proc. Natl. Acad.</i> transcarbamoylase <i>Sci. U.S.A.</i> 90 :11980-11984, 1993).
30	phosphoribosyl anthranilate	Luger et al., Science 243 :206-210 (1989; Luger et al., Prot. Eng. Isomerase 3 :249-258, 1990).
35	pepsin/pepsinogen	Lin et al., <i>Protein Science</i> 4 :159-166, 1995).
	glyceraldehyde-3- phosphate dehydro- genase	Vignais et al., <i>Protein Science</i> 4 :994-1000, 1995).
40	ornithine	Li & Coffino, Mol. Cell. Biol.

decarboxylase 13:2377-2383, 1993).

yeast phosphoglycerate dehydrogenase Ritco-Vonsovici et al., Biochemistry **34**:16543-16551, 1995).

Enzyme Inhibitor

basic pancreatic Goldenberg & Creighton, J. Mol. trypsin inhibitor Biol. 165:407-413, 1983).

Cytokines

interleukin-1b Horlick et al., Protein Eng. 5:427-431, 1992).

interleukin-4 Kreitman et al., Cytokine 7:311-318, 1995).

20 Tyrosine Kinase Recognition Domain

a-spectrin SH3 Viguera, et al., *J. Mol. Biol.* domain **247**:670-681, 1995).

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Transmembrane Protein

omp A Koebnik & Krämer, *J. Mol. Biol.* **250**:617-626, 1995).

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Chimeric Protein

interleukin-4- Kreitman et al., *Proc. Natl. Acad. Pseudomonas* Sci. U.S.A. **91**:6889-6893, 1994).

exotoxin

[0017] The results of these studies have been highly variable. Ιn many cases substantially lower activity, solubility or thermodynamic stability were observed (E. coli 40 dihydrofolate reductase, aspartate transcarbamoylase, phosphoribosyl anthranilate isomerase, glyceraldehyde-3phosphate dehydrogenase, ornithine decarboxylase, omp A, yeast

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phosphoglycerate dehydrogenase). In other cases, the sequence rearranged protein appeared to have many nearly identical properties as its natural counterpart (basic pancreatic trypsin inhibitor, T4 lysozyme, ribonuclease T1, Bacillus bglucanase, interleukin-1b, a-spectrin SH3 domain, pepsinogen, interleukin-4). exceptional cases, In an unexpected improvement over some properties of the natural sequence was observed, e.q., the solubility and refolding rate rearranged a-spectrin SH3 domain sequences, and the receptor affinity and anti-tumor activity of transposed interleukin-4-Pseudomonas exotoxin fusion molecule (Kreitman et al., Proc. Natl. Acad. Sci. U.S.A. 91:6889-6893, 1994; Kreitman et al., Cancer Res. 55:3357-3363, 1995).

has been to study the role of short-range and long-range interactions in protein folding and stability. Sequence rearrangements of this type convert a subset of interactions that are long-range in the original sequence into short-range interactions in the new sequence, and vice versa. The fact that many of these sequence rearrangements are able to attain a conformation with at least some activity is persuasive evidence that protein folding occurs by multiple folding pathways (Viguera, et al., *J. Mol. Biol.* 247:670-681, 1995). In the case of the SH3 domain of a-spectrin, choosing new

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termini at locations that corresponded to b-hairpin turns resulted in proteins with slightly less stability, but which were nevertheless able to fold.

The positions of the internal breakpoints used in the studies cited here are found exclusively on the surface of proteins, and are distributed throughout the linear sequence without any obvious bias towards the ends or the middle (the variation in the relative distance from the original Nterminus to the breakpoint is ca. 10 to 80% of the total sequence length). The linkers connecting the original N- and C-termini in these studies have ranged from 0 to 9 residues. In one case (Yang & Schachman, Proc. Natl. Acad. Sci. U.S.A. 90:11980-11984, 1993), a portion of sequence has been deleted from the original C-terminal segment, and the connection made from the truncated C-terminus to the original N-terminus. hydrophilic residues such as Gly and Ser are Flexible frequently used in the linkers. Viguera, et al. (J. Mol. Biol. **247**:670-681, 1995) compared joining the original N- and Ctermini with 3- or 4-residue linkers; the 3-residue linker was less thermodynamically stable. Protasova et al. (Protein Eng. 7:1373-1377, 1994) used 3- or 5-residue linkers in connecting the original N-termini of E. coli dihydrofolate reductase; only the 3-residue linker produced protein in good yield.

BRIEF SUMMARY OF THE INVENTION

[0020] Novel hematopoietic proteins of this invention are represented by the formulas:

5 $R_1-L_1-R_2$, $R_2-L_1-R_1$, R_1-R_2 , or R_2-R_1

wherein R_1 and R_2 are independently selected from the group consisting of;

(I) A polypeptide comprising; a modified human G-CSF amino acid sequence of the formula:

10 Xaa Xaa Xaa Gly Pro Ala Ser Ser Leu Pro Gln Ser Xaa 5 20 Leu Leu Xaa Xaa Glu Gln Val Xaa Lys Xaa Gln Gly Xaa Gly 30 10 Ala Xaa Leu Gln Glu Xaa Leu Xaa Ala Thr Tyr Lys Leu Xaa Xaa 50 Xaa Glu Xaa Xaa Val Xaa Xaa Gly His Ser Xaa Gly Ile Pro Trp 15 60 70 Ala Pro Leu Ser Ser Xaa Pro Ser Xaa Ala Leu Xaa Leu Ala Gly 80 Xaa Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu 20 Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu 110 25 Xaa Thr Leu Gln Xaa Asp Val Ala Asp Phe Ala Xaa Thr Ile Trp 120 130 Gln Gln Met Glu Xaa Xaa Gly Met Ala Pro Ala Leu Gln Pro Thr 30 140 Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Xaa Gln Xaa Xaa Ala 150 160 Gly Gly Val Leu Val Ala Ser Xaa Leu Gln Xaa Phe Leu Xaa Xaa 35 Ser Tyr Arg Val Leu Xaa Xaa Leu Ala Gln Pro (SEQ ID NO:1) wherein 40 Xaa at position 1 is Thr, Ser, Arg, Tyr or Gly; Xaa at position 2 is Pro or Leu; Xaa at position 3 is Leu, Arg, Tyr or Ser;

Xaa at position 13 is Phe, Ser, His, Thr or Pro;

Xaa at position 16 is Lys, Pro, Ser, Thr or His;

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Xaa at position 17 is Cys, Ser, Gly, Ala, Ile, Tyr or
    Xaa at position 18 is Leu, Thr, Pro, His, Ile or Cys;
    Xaa at position 22 is Arg, Tyr, Ser, Thr or Ala;
   Xaa at position 24 is Ile, Pro, Tyr or Leu;
   Xaa at position 27 is Asp, or Gly;
   Xaa at position 30 is Ala, Ile, Leu or Gly;
    Xaa at position 34 is Lys or Ser;
    Xaa at position 36 is Cys or Ser;
    Xaa at position 42 is Cys or Ser;
10
   Xaa at position 43 is His, Thr, Gly, Val, Lys, Trp, Ala,
         Arg, Cys, or Leu;
    Xaa at position 44 is Pro, Gly, Arg, Asp, Val, Ala, His,
         Trp, Gln, or Thr;
    Xaa at position 46 is Glu, Arg, Phe, Arg, Ile or Ala;
15
   Xaa at position 47 is Leu or Thr;
    Xaa at position 49 is Leu, Phe, Arg or Ser;
    Xaa at position 50 is Leu, Ile, His, Pro or Tyr;
    Xaa at position 54 is Leu or His;
    Xaa at position 64 is Cys or Ser;
20
   Xaa at position 67 is Gln, Lys, Leu or Cys;
    Xaa at position 70 is Gln, Pro, Leu, Arg or Ser;
    Xaa at position 74 is Cys or Ser;
    Xaa at position 104 is Asp, Gly or Val;
    Xaa at position 108 is Leu, Ala, Val, Arg, Trp, Gln or
25
         Gly;
    Xaa at position 115 is Thr, His, Leu or Ala;
    Xaa at position 120 is Gln, Gly, Arg, Lys or His
    Xaa at position 123 is Glu, Arg, Phe or Thr
    Xaa at position 144 is Phe, His, Arg, Pro, Leu, Gln or
30
         Glu;
    Xaa at position 146 is Arg or Gln;
    Xaa at position 147 is Arg or Gln;
    Xaa at position 156 is His, Gly or Ser;
    Xaa at position 159 is Ser, Arg, Thr, Tyr, Val or Gly;
35
   Xaa at position 162 is Glu, Leu, Gly or Trp;
    Xaa at position 163 is Val, Gly, Arg or Ala;
    Xaa at position 169 is Arg, Ser, Leu, Arg or Cys;
    Xaa at position 170 is His, Arg or Ser;
40
   wherein optionally 1-11 amino acids from the N-terminus and 1-
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5 from the C-terminus can be deleted; and wherein the N-terminus is joined to the C-terminus directly or through a linker capable of joining the N-terminus to the C-

terminus and having new C- and N-termini at amino acids;

	38-39	62-63	123-124
	39-40	63-64	124-125
	40-41	64-65	125-126
5	41-42	65-66	126-127
	42-43	66-67	128-129
	43-44	67-68	128-129
	45-46	68-69	129-130
	48-49	69-70	130-131
10	49-50	70-71	131-132
	52-53	71-72	132-133
	53-54	91-92	133-134
	54-55	92-93	134-135
	55-56	93-94	135-136
15	56-57	94-95	136-137
	57-58	95-96	137-138
	58-59	96-97	138-139
	59-60	97-98	139-140
	60-61	98-99	140-141
20	61-62	99-100	141-142
			or 142-143;

(II) A polypeptide comprising; a modified hIL-3 amino acid sequence of the formula:

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Ala Pro Met Thr Gln Thr Thr Ser Leu Lys Thr Ser Trp Val Asn
                 10
5
 25
 Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asn Xaa Xaa Xaa Xaa Xaa
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        35
                 40
                         45
 50
                 55
                         60
15
 65
                         75
 80
                 85
                         90
20
 100
 25
        110
                 115
                         120
 Xaa Xaa Xaa Gln Gln Thr Thr Leu Ser Leu Ala Ile Phe
        125
                 130
                   (SEQ ID NO:2);
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30 wherein

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Xaa at position 17 is Ser, Lys, Gly, Asp, Met, Gln, or Arg;
    Xaa at position 18 is Asn, His, Leu, Ile, Phe, Arg, or Gln;
    Xaa at position 19 is Met, Phe, Ile, Arg, Gly, Ala, or Cys;
    Xaa at position 20 is Ile, Cys, Gln, Glu, Arg, Pro, or Ala;
    Xaa at position 21 is Asp, Phe, Lys, Arg, Ala, Gly, Glu, Gln,
35
         Asn, Thr, Ser or Val;
    Xaa at position 22 is Glu, Trp, Pro, Ser, Ala, His, Asp, Asn,
         Gln, Leu, Val or Gly;
    Xaa at position 23 is Ile, Val, Ala, Gly, Trp, Lys, Phe, Leu,
40
         Ser, or Arq;
    Xaa at position 24 is Ile, Gly, Val, Arg, Ser, Phe, or Leu;
    Xaa at position 25 is Thr, His, Gly, Gln, Arg, Pro, or Ala;
    Xaa at position 26 is His, Thr, Phe, Gly, Arg, Ala, or Trp;
    Xaa at position 27 is Leu, Gly, Arg, Thr, Ser, or Ala;
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Xaa at position 28 is Lys, Arg, Leu, Gln, Gly, Pro, Val or
         Trp;
    Xaa at position 29 is Gln, Asn, Leu, Pro, Arg, or Val;
    Xaa at position 30 is Pro, His, Thr, Gly, Asp, Gln, Ser, Leu,
5
                  Lys;
         or
    Xaa at position 31 is Pro, Asp, Gly, Ala, Arg, Leu, or Gln;
    Xaa at position 32 is Leu, Val, Arg, Gln, Asn, Gly, Ala, or
    Xaa at position 33 is Pro, Leu, Gln, Ala, Thr, or Glu;
    Xaa at position 34 is Leu, Val, Gly, Ser, Lys, Glu, Gln,
10
         Thr, Arg, Ala, Phe, Ile or Met;
    Xaa at position 35 is Leu, Ala, Gly, Asn, Pro, Gln, or Val;
    Xaa at position 36 is Asp, Leu, or Val;
    Xaa at position 37 is Phe, Ser, Pro, Trp, or Ile;
15
    Xaa at position 38 is Asn, or Ala;
    Xaa at position 40 is Leu, Trp, or Arg;
    Xaa at position 41 is Asn, Cys, Arg, Leu, His, Met, or Pro;
    Xaa at position 42 is Gly, Asp, Ser, Cys, Asn, Lys, Thr, Leu,
         Val, Glu, Phe, Tyr, Ile, Met or Ala;
20
    Xaa at position 43 is Glu, Asn, Tyr, Leu, Phe, Asp, Ala,
         Cys, Gln, Arg, Thr, Gly or Ser;
    Xaa at position 44 is Asp, Ser, Leu, Arg, Lys, Thr, Met, Trp,
         Glu, Asn, Gln, Ala or Pro;
    Xaa at position 45 is Gln, Pro, Phe, Val, Met, Leu, Thr, Lys,
25
         Trp, Asp, Asn, Arg, Ser, Ala, Ile, Glu or His;
    Xaa at position 46 is Asp, Phe, Ser, Thr, Cys, Glu, Asn, Gln,
         Lys, His, Ala, Tyr, Ile, Val or Gly;
    Xaa at position 47 is Ile, Gly, Val, Ser, Arg, Pro, or His;
    Xaa at position 48 is Leu, Ser, Cys, Arg, Ile, His, Phe, Glu,
30
         Lys, Thr, Ala, Met, Val or Asn;
    Xaa at position 49 is Met, Arg, Ala, Gly, Pro, Asn, His, or
         Asp;
    Xaa at position 50 is Glu, Leu, Thr, Asp, Tyr, Lys, Asn, Ser,
         Ala, Ile, Val, His, Phe, Met or Gln;
35
    Xaa at position 51 is Asn, Arg, Met, Pro, Ser, Thr, or His;
    Xaa at position 52 is Asn, His, Arg, Leu, Gly, Ser, or Thr;
    Xaa at position 53 is Leu, Thr, Ala, Gly, Glu, Pro, Lys, Ser,
                  Met;
         or
    Xaa at position 54 is Arg, Asp, Ile, Ser, Val, Thr, Gln, Asn,
40
         Lys, His, Ala or Leu;
    Xaa at position 55 is Arg, Thr, Val, Ser, Leu, or Gly;
    Xaa at position 56 is Pro, Gly, Cys, Ser, Gln, Glu, Arg, His,
         Thr, Ala, Tyr, Phe, Leu, Val or Lys;
    Xaa at position 57 is Asn or Gly;
45
    Xaa at position 58 is Leu, Ser, Asp, Arg, Gln, Val, or Cys;
    Xaa at position 59 is Glu Tyr, His, Leu, Pro, or Arg;
    Xaa at position 60 is Ala, Ser, Pro, Tyr, Asn, or Thr;
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Xaa at position 61 is Phe, Asn, Glu, Pro, Lys, Arg, or Ser;
    Xaa at position 62 is Asn, His, Val, Arg, Pro, Thr, Asp, or
         Ile;
    Xaa at position 63 is Arg, Tyr, Trp, Lys, Ser, His, Pro, or
 5
         Val;
    Xaa at position 64 is Ala, Asn, Pro, Ser, or Lys;
    Xaa at position 65 is Val, Thr, Pro, His, Leu, Phe, or Ser;
    Xaa at position 66 is Lys, Ile, Arg, Val, Asn, Glu, or Ser;
    Xaa at position 67 is Ser, Ala, Phe, Val, Gly, Asn, Ile, Pro,
10
         or
                  His;
    Xaa at position 68 is Leu, Val, Trp, Ser, Ile, Phe, Thr, or
         His;
    Xaa at position 69 is Gln, Ala, Pro, Thr, Glu, Arg, Trp, Gly,
                  Leu;
15
    Xaa at position 70 is Asn, Leu, Val, Trp, Pro, or Ala;
    Xaa at position 71 is Ala, Met, Leu, Pro, Arg, Glu, Thr, Gln,
         Trp, or Asn;
    Xaa at position 72 is Ser, Glu, Met, Ala, His, Asn, Arg, or
20
    Xaa at position 73 is Ala, Glu, Asp, Leu, Ser, Gly, Thr, or
    Xaa at position 74 is Ile, Met, Thr, Pro, Arg, Gly, Ala;
    Xaa at position 75 is Glu, Lys, Gly, Asp, Pro, Trp, Arg, Ser,
         Gln, or Leu;
25
    Xaa at position 76 is Ser, Val, Ala, Asn, Trp, Glu, Pro, Gly,
         or
                  Asp;
    Xaa at position 77 is Ile, Ser, Arg, Thr, or Leu;
    Xaa at position 78 is Leu, Ala, Ser, Glu, Phe, Gly, or Arg;
    Xaa at position 79 is Lys, Thr, Asn, Met, Arg, Ile, Gly, or
30
         Asp;
    Xaa at position 80 is Asn, Trp, Val, Gly, Thr, Leu, Glu, or
    Xaa at position 81 is Leu, Gln, Gly, Ala, Trp, Arg, Val, or
         Lys;
35
    Xaa at position 82 is Leu, Gln, Lys, Trp, Arg, Asp, Glu, Asn,
         His, Thr, Ser, Ala, Tyr, Phe, Ile, Met or Val;
    Xaa at position 83 is Pro, Ala, Thr, Trp, Arg, or Met;
    Xaa at position 84 is Cys, Glu, Gly, Arg, Met, or Val;
    Xaa at position 85 is Leu, Asn, Val, or Gln;
40
    Xaa at position 86 is Pro, Cys, Arg, Ala, or Lys;
    Xaa at position 87 is Leu, Ser, Trp, or Gly;
    Xaa at position 88 is Ala, Lys, Arg, Val, or Trp;
    Xaa at position 89 is Thr, Asp, Cys, Leu, Val, Glu, His, Asn,
         or
                  Ser;
45
    Xaa at position 90 is Ala, Pro, Ser, Thr, Gly, Asp, Ile, or
    Xaa at position 91 is Ala, Pro, Ser, Thr, Phe, Leu, Asp, or
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His;
    Xaa at position 92 is Pro, Phe, Arg, Ser, Lys, His, Ala, Gly,
         Ile or Leu;
    Xaa at position 93 is Thr, Asp, Ser, Asn, Pro, Ala, Leu, or
5
         Arq;
    Xaa at position 94 is Arg, Ile, Ser, Glu, Leu, Val, Gln, Lys,
         His, Ala, or Pro;
    Xaa at position 95 is His, Gln, Pro, Arg, Val, Leu, Gly, Thr,
         Asn, Lys, Ser, Ala, Trp, Phe, Ile, or Tyr;
10
    Xaa at position 96 is Pro, Lys, Tyr, Gly, Ile, or Thr;
    Xaa at position 97 is Ile, Val, Lys, Ala, or Asn;
    Xaa at position 98 is His, Ile, Asn, Leu, Asp, Ala, Thr, Glu,
         Gln, Ser, Phe, Met, Val, Lys, Arg, Tyr or Pro;
    Xaa at position 99 is Ile, Leu, Arg, Asp, Val, Pro, Gln, Gly,
15
         Ser, Phe, or His;
    Xaa at position 100 is Lys, Tyr, Leu, His, Arg, Ile, Ser, Gln,
         or Pro;
    Xaa at position 101 is Asp, Pro, Met, Lys, His, Thr, Val, Tyr,
         Glu, Asn, Ser, Ala, Gly, Ile, Leu, or Gln;
    Xaa at position 102 is Gly, Leu, Glu, Lys, Ser, Tyr, or Pro;
20
    Xaa at position 103 is Asp, or Ser;
    Xaa at position 104 is Trp, Val, Cys, Tyr, Thr, Met, Pro, Leu,
         Gln, Lys, Ala, Phe, or Gly;
    Xaa at position 105 is Asn, Pro, Ala, Phe, Ser, Trp, Gln, Tyr,
25
         Leu, Lys, Ile, Asp, or His;
    Xaa at position 106 is Glu, Ser, Ala, Lys, Thr, Ile, Gly, or
         Pro;
    Xaa at position 108 is Arg, Lys, Asp, Leu, Thr, Ile, Gln, His,
         Ser, Ala or Pro;
30
    Xaa at position 109 is Arg, Thr, Pro, Glu, Tyr, Leu, Ser, or
    Xaa at position 110 is Lys, Ala, Asn, Thr, Leu, Arg, Gln, His,
         Glu, Ser, or Trp;
    Xaa at position 111 is Leu, Ile, Arg, Asp, or Met;
35
    Xaa at position 112 is Thr, Val, Gln, Tyr, Glu, His, Ser, or
    Xaa at position 113 is Phe, Ser, Cys, His, Gly, Trp, Tyr, Asp,
         Lys, Leu, Ile, Val or Asn;
    Xaa at position 114 is Tyr, Cys, His, Ser, Trp, Arg, or Leu;
40
    Xaa at position 115 is Leu, Asn, Val, Pro, Arg, Ala, His, Thr,
         Trp, or Met;
    Xaa at position 116 is Lys, Leu, Pro, Thr, Met, Asp, Val, Glu,
         Arg, Trp, Ser, Asn, His, Ala, Tyr, Phe, Gln, or Ile;
    Xaa at position 117 is Thr, Ser, Asn, Ile, Trp, Lys, or Pro;
45
    Xaa at position 118 is Leu, Ser, Pro, Ala, Glu, Cys, Asp, or
         Tyr;
    Xaa at position 119 is Glu, Ser, Lys, Pro, Leu, Thr, Tyr, or
```

Arg;

Xaa at position 120 is Asn, Ala, Pro, Leu, His, Val, or Gln; Xaa at position 121 is Ala, Ser, Ile, Asn, Pro, Lys, Asp, or Gly;

- 5 Xaa at position 122 is Gln, Ser, Met, Trp, Arg, Phe, Pro, His, Ile, Tyr, or Cys;
 - Xaa at position 123 is Ala, Met, Glu, His, Ser, Pro, Tyr, or Leu;
- 10 wherein optionally from 1 to 14 amino acids can be deleted from the N-terminus and/or from 1 to 15 amino acids can be deleted from the C-terminus; and wherein from 0 to 44 of the amino acids designated by Xaa are different from the corresponding amino acids of native (1-133) human interleukin-
- 15 3; and

wherein the N-terminus is joined to the C-terminus directly or through a linker (L2) capable of joining the N-terminus to the C-terminus and having new C- and N-termini at amino acids;

	26-27	49-50	83-84
20	27-28	50-51	84-85
	28-29	51-52	85-86
	29-30	52-53	86-87
	30-31	53-54	87-88
	31-32	54-55	88-89
25	32-33	64-65	89-90
	33-34	65-66	90-91
	34-35	66-67	91-92
	35-36	67-68	92-93
	36-37	68-69	97-98
30	37-38	69-70	98-99
	38-39	70-71	99-100
	39-40	71-72	100-101
	40-41	72-73	101-102
	41-42	82-83	102-103
35			or 103-104;

or

	(III)	A polypepti	de compri	sing; a	modified	human	c-mpl
	ligand amino	acid seque	nce of the	e formula	a:		
5	SerProAlaPro	ProAlaCysAs 5	pLeuArgVa 10	lLeuSerLy	ysLeuLeuAr 15	gAspSer	
J	HisValLeuHis 20	SerArgLeuSe 25	rGlnCysPr 30	oGluValH:	isProLeuPr 35	oThrPro	•
0	ValLeuLeuPro 40	AlaValAspPh 45	eSerLeuGl	yGluTrpLy 50	ysThrGlnMe 55		ı
	ThrLysAlaGlr 60	AspIleLeuGl 65		rLeuLeuLe 70	euGluGlyVa	lMetAla 75	ı
15	AlaArgGlyGlr 80	ıLeuGlyProTh	rCysLeuSe 85	rSerLeuLe 90	-	uSerGly 95	,
20	GlnValArgLeu	LeuLeuGlyAl 100	aLeuGlnSe 105	rLeuLeuG	lyThrGlnXa 110	aXaaXaa	L
	XaaGlyArgThr 115	ThrAlaHisLy 120	sAspProAs 12		neLeuSerPh 130	eGlnHis	:
25	LeuLeuArgGly	LysValArgPh 140	eLeuMetLe	uValGlyG 145	lySerThrLe 15		
	ArgArgAlaPro	ProThrThrAl		rArgThrSe 165	erLeuValLe	uThrLeu 170	l
30	AsnGluLeuPro	_	rGlyLeuLe 180		snPheThrAl 35	aSerAla 190	
	ArgThrThrGly	SerGlyLeuLe 195	uLysTrpGl 200	nGlnGlyPl	neArgAlaLy 205	sIlePro	,
35	GlyLeuLeuAsr 210	GlnThrSerAr 215	gSerLeuAs 22	-	roGlyTyrLe 225	uAsnArg	ī
10	IleHisGluLeu 230	ıLeuAsnGlyTh 235	rArgGlyLe	uPheProG 240	lyProSerAr 24		
	LeuGlyAlaPro	AspIleSerSe 25	_	rAspThrG	lySerLeuPr	oProAsn 265	L
15	LeuGlnProGly	TvrSerProSe	rProThrHi	sProProT}	nrGlyGlnTy	rThrLeu	ı

270 275 280 285

PheProLeuProThrLeuProThrProValValGlnLeuHisProLeuLeuPro 290 295 300

AspProSerAlaProThrProThrProThrSerProLeuLeuAsnThrSerTyrThr 305 310 315 320

HisSerGlnAsnLeuSerGlnGluGly (SEQ ID NO:3) 325 330 332 153

wherein;

5

10

- 15 Xaa at position 112 is deleted or Leu, Ala, Val, Ile, Pro, Phe, Trp, or Met;
 Xaa at position 113 is deleted or Pro, Phe, Ala, Val, Leu, Ile, Trp, or Met;
 Xaa at position 114 is deleted or Pro, Phe, Ala, Val, Leu, Ile, Trp, or Met;
 - Ile, Trp, or Met; Xaa at position 115 is deleted or Gln, Gly, Ser, Thr, Tyr, or Asn; and
- wherein the N-terminus is joined to the C-terminus directly or through a linker (L2) capable of joining the N-terminus to the C-terminus and having new C- and N-termini at amino acids;

or

	26-27	51-52	108-109
	27-28	52-53	109-110
	28-29	53-54	110-111
	29-30	54-55	111-112
5	30-31	55-56	112-113
	32-33	56-57	113-114
	33-34	57-58	114-115
	34-35	58-59	115-116
	36-37	59-60	116-117
10	37-38	78-79	117-118
	38-39	79-80	118-119
	40-41	80-81	119-120
	41-42	81-82	120-121
	42-43	82-83	121-122
15	43-44	83-84	122-123
	44-45	84-85	123-124
	46-47	85-86	124-125
	47-48	86-87	125-126
	48-49	87-88	126-127
20	50-51	88-89	or 127-128;

(IV) A polypeptide comprising; a modified hIL-3 amino acid sequence of the formula:

Ala Pro Met Thr Gln Thr Thr Ser Leu Lys Thr Ser Trp Val Asn
1 5 10 15

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asn Xaa Xaa Xaa Xaa Xaa 35 40 45

30 wherein

5

10

20

Xaa at position 17 is Ser, Lys, Gly, Asp, Met, Gln, or Arg;

Xaa at position 18 is Asn, His, Leu, Ile, Phe, Arg, or Gln;

Xaa at position 19 is Met, Phe, Ile, Arg, Gly, Ala, or Cys; 35 Xaa at position 20 is Ile, Cys, Gln, Glu, Arg, Pro, or Ala;

Xaa at position 21 is Asp, Phe, Lys, Arg, Ala, Gly, Glu, Gln, Asn, Thr, Ser or Val;

Xaa at position 22 is Glu, Trp, Pro, Ser, Ala, His, Asp, Asn, Gln, Leu, Val or Gly;

40 Xaa at position 23 is Ile, Val, Ala, Gly, Trp, Lys, Phe, Leu, Ser, or Arg;

Xaa at position 24 is Ile, Gly, Val, Arg, Ser, Phe, or Leu;

Xaa at position 25 is Thr, His, Gly, Gln, Arg, Pro, or Ala;

Xaa at position 26 is His, Thr, Phe, Gly, Arg, Ala, or Trp; 45 Xaa at position 27 is Leu, Gly, Arg, Thr, Ser, or Ala;

```
Xaa at position 28 is Lys, Arg, Leu, Gln, Gly, Pro, Val or
         Trp;
    Xaa at position 29 is Gln, Asn, Leu, Pro, Arq, or Val;
    Xaa at position 30 is Pro, His, Thr, Gly, Asp, Gln, Ser, Leu,
5
         or Lys;
    Xaa at position 31 is Pro, Asp, Gly, Ala, Arg, Leu, or Gln;
    Xaa at position 32 is Leu, Val, Arg, Gln, Asn, Gly, Ala, or
    Xaa at position 33 is Pro, Leu, Gln, Ala, Thr, or Glu;
10
    Xaa at position 34 is Leu, Val, Gly, Ser, Lys, Glu, Gln, Thr,
         Arg, Ala, Phe, Ile or Met;
    Xaa at position 35 is Leu, Ala, Gly, Asn, Pro, Gln, or Val;
    Xaa at position 36 is Asp, Leu, or Val;
    Xaa at position 37 is Phe, Ser, Pro, Trp, or Ile;
15
    Xaa at position 38 is Asn, or Ala;
    Xaa at position 40 is Leu, Trp, or Arg;
    Xaa at position 41 is Asn, Cys, Arg, Leu, His, Met, or Pro;
    Xaa at position 42 is Gly, Asp, Ser, Cys, Asn, Lys, Thr, Leu,
         Val, Glu, Phe, Tyr, Ile, Met or Ala;
20
    Xaa at position 43 is Glu, Asn, Tyr, Leu, Phe, Asp, Ala, Cys,
         Gln, Arg, Thr, Gly or Ser;
    Xaa at position 44 is Asp, Ser, Leu, Arg, Lys, Thr, Met, Trp,
         Glu, Asn, Gln, Ala or Pro;
    Xaa at position 45 is Gln, Pro, Phe, Val, Met, Leu, Thr, Lys,
25
         Trp, Asp, Asn, Arg, Ser, Ala, Ile, Glu or His;
    Xaa at position 46 is Asp, Phe, Ser, Thr, Cys, Glu, Asn, Gln,
         Lys, His, Ala, Tyr, Ile, Val or Gly;
    Xaa at position 47 is Ile, Gly, Val, Ser, Arg, Pro, or His;
    Xaa at position 48 is Leu, Ser, Cys, Arg, Ile, His, Phe, Glu,
30
         Lys, Thr, Ala, Met, Val or Asn;
    Xaa at position 49 is Met, Arg, Ala, Gly, Pro, Asn, His, or
         Asp;
    Xaa at position 50 is Glu, Leu, Thr, Asp, Tyr, Lys, Asn, Ser,
         Ala, Ile, Val, His, Phe, Met or Gln;
35
    Xaa at position 51 is Asn, Arg, Met, Pro, Ser, Thr, or His;
    Xaa at position 52 is Asn, His, Arg, Leu, Gly, Ser, or Thr;
    Xaa at position 53 is Leu, Thr, Ala, Gly, Glu, Pro, Lys, Ser,
         or Met;
    Xaa at position 54 is Arg, Asp, Ile, Ser, Val, Thr, Gln, Asn,
40
         Lys, His, Ala or Leu;
    Xaa at position 55 is Arg, Thr, Val, Ser, Leu, or Gly;
    Xaa at position 56 is Pro, Gly, Cys, Ser, Gln, Glu, Arg, His,
         Thr, Ala, Tyr, Phe, Leu, Val or Lys;
    Xaa at position 57 is Asn or Gly;
45
    Xaa at position 58 is Leu, Ser, Asp, Arg, Gln, Val, or Cys;
    Xaa at position 59 is Glu Tyr, His, Leu, Pro, or Arg;
    Xaa at position 60 is Ala, Ser, Pro, Tyr, Asn, or Thr;
```

```
Xaa at position 61 is Phe, Asn, Glu, Pro, Lys, Arg, or Ser;
    Xaa at position 62 is Asn, His, Val, Arg, Pro, Thr, Asp, or
         Ile;
    Xaa at position 63 is Arg, Tyr, Trp, Lys, Ser, His, Pro, or
 5
         Val;
    Xaa at position 64 is Ala, Asn, Pro, Ser, or Lys;
    Xaa at position 65 is Val, Thr, Pro, His, Leu, Phe, or Ser;
    Xaa at position 66 is Lys, Ile, Arg, Val, Asn, Glu, or Ser;
    Xaa at position 67 is Ser, Ala, Phe, Val, Gly, Asn, Ile, Pro,
10
         or His;
    Xaa at position 68 is Leu, Val, Trp, Ser, Ile, Phe, Thr, or
         His;
    Xaa at position 69 is Gln, Ala, Pro, Thr, Glu, Arg, Trp, Gly,
         or Leu;
15
    Xaa at position 70 is Asn, Leu, Val, Trp, Pro, or Ala;
    Xaa at position 71 is Ala, Met, Leu, Pro, Arg, Glu, Thr, Gln,
         Trp, or Asn;
    Xaa at position 72 is Ser, Glu, Met, Ala, His, Asn, Arg, or
20
    Xaa at position 73 is Ala, Glu, Asp, Leu, Ser, Gly, Thr, or
         Arq;
    Xaa at position 74 is Ile, Met, Thr, Pro, Arg, Gly, Ala;
    Xaa at position 75 is Glu, Lys, Gly, Asp, Pro, Trp, Arg, Ser,
         Gln, or Leu;
25
    Xaa at position 76 is Ser, Val, Ala, Asn, Trp, Glu, Pro, Gly,
         or Asp;
    Xaa at position 77 is Ile, Ser, Arg, Thr, or Leu;
    Xaa at position 78 is Leu, Ala, Ser, Glu, Phe, Gly, or Arg;
    Xaa at position 79 is Lys, Thr, Asn, Met, Arg, Ile, Gly, or
30
         Asp;
    Xaa at position 80 is Asn, Trp, Val, Gly, Thr, Leu, Glu, or
    Xaa at position 81 is Leu, Gln, Gly, Ala, Trp, Arg, Val, or
         Lys;
    Xaa at position 82 is Leu, Gln, Lys, Trp, Arg, Asp, Glu, Asn,
35
         His, Thr, Ser, Ala, Tyr, Phe, Ile, Met or Val;
    Xaa at position 83 is Pro, Ala, Thr, Trp, Arg, or Met;
    Xaa at position 84 is Cys, Glu, Gly, Arg, Met, or Val;
    Xaa at position 85 is Leu, Asn, Val, or Gln;
40
    Xaa at position 86 is Pro, Cys, Arg, Ala, or Lys;
    Xaa at position 87 is Leu, Ser, Trp, or Gly;
    Xaa at position 88 is Ala, Lys, Arg, Val, or Trp;
    Xaa at position 89 is Thr, Asp, Cys, Leu, Val, Glu, His, Asn,
         or Ser;
45
    Xaa at position 90 is Ala, Pro, Ser, Thr, Gly, Asp, Ile, or
         Met;
    Xaa at position 91 is Ala, Pro, Ser, Thr, Phe, Leu, Asp, or
```

```
His;
    Xaa at position 92 is Pro, Phe, Arg, Ser, Lys, His, Ala, Gly,
         Ile or Leu;
    Xaa at position 93 is Thr, Asp, Ser, Asn, Pro, Ala, Leu, or
5
         Arq;
    Xaa at position 94 is Arg, Ile, Ser, Glu, Leu, Val, Gln, Lys,
         His, Ala, or Pro;
    Xaa at position 95 is His, Gln, Pro, Arg, Val, Leu, Gly, Thr,
         Asn, Lys, Ser, Ala, Trp, Phe, Ile, or Tyr;
10
    Xaa at position 96 is Pro, Lys, Tyr, Gly, Ile, or Thr;
    Xaa at position 97 is Ile, Val, Lys, Ala, or Asn;
Xaa at position 98 is His, Ile, Asn, Leu, Asp, Ala, Thr, Glu,
         Gln, Ser, Phe, Met, Val, Lys, Arg, Tyr or Pro;
    Xaa at position 99 is Ile, Leu, Arg, Asp, Val, Pro, Gln, Gly,
15
         Ser, Phe, or His;
    Xaa at position 100 is Lys, Tyr, Leu, His, Arg, Ile, Ser, Gln,
         or Pro;
    Xaa at position 101 is Asp, Pro, Met, Lys, His, Thr, Val, Tyr,
         Glu, Asn, Ser, Ala, Gly, Ile, Leu, or Gln;
    Xaa at position 102 is Gly, Leu, Glu, Lys, Ser, Tyr, or Pro;
20
    Xaa at position 103 is Asp, or Ser;
    Xaa at position 104 is Trp, Val, Cys, Tyr, Thr, Met, Pro, Leu,
         Gln, Lys, Ala, Phe, or Gly;
    Xaa at position 105 is Asn, Pro, Ala, Phe, Ser, Trp, Gln, Tyr,
25
         Leu, Lys, Ile, Asp, or His;
    Xaa at position 106 is Glu, Ser, Ala, Lys, Thr, Ile, Gly, or
         Pro;
    Xaa at position 108 is Arg, Lys, Asp, Leu, Thr, Ile, Gln, His,
         Ser, Ala or Pro;
30
    Xaa at position 109 is Arg, Thr, Pro, Glu, Tyr, Leu, Ser, or
         Gly;
    Xaa at position 110 is Lys, Ala, Asn, Thr, Leu, Arg, Gln, His,
         Glu, Ser, or Trp;
    Xaa at position 111 is Leu, Ile, Arg, Asp, or Met;
35
    Xaa at position 112 is Thr, Val, Gln, Tyr, Glu, His, Ser, or
    Xaa at position 113 is Phe, Ser, Cys, His, Gly, Trp, Tyr, Asp,
         Lys, Leu, Ile, Val or Asn;
    Xaa at position 114 is Tyr, Cys, His, Ser, Trp, Arg, or Leu;
40
    Xaa at position 115 is Leu, Asn, Val, Pro, Arg, Ala, His, Thr,
         Trp, or Met;
    Xaa at position 116 is Lys, Leu, Pro, Thr, Met, Asp, Val, Glu,
         Arg, Trp, Ser, Asn, His, Ala, Tyr, Phe, Gln, or Ile;
    Xaa at position 117 is Thr, Ser, Asn, Ile, Trp, Lys, or Pro;
45
    Xaa at position 118 is Leu, Ser, Pro, Ala, Glu, Cys, Asp, or
         Tyr;
    Xaa at position 119 is Glu, Ser, Lys, Pro, Leu, Thr, Tyr, or
```

Arg;

Xaa at position 120 is Asn, Ala, Pro, Leu, His, Val, or Gln; Xaa at position 121 is Ala, Ser, Ile, Asn, Pro, Lys, Asp, or Gly;

- 5 Xaa at position 122 is Gln, Ser, Met, Trp, Arg, Phe, Pro, His, Ile, Tyr, or Cys;
 - Xaa at position 123 is Ala, Met, Glu, His, Ser, Pro, Tyr, or Leu;
- 10 wherein optionally from 1 to 14 amino acids can be deleted from the N-terminus and/or from 1 to 15 amino acids can be deleted from the C-terminus; and wherein from 1 to 44 of the amino acids designated by Xaa are different from the corresponding amino acids of native (1-133) human interleukin-
- 15 3;

or

(V) a colony stimulating factor;

and wherein L1 is a linker capable of linking R1 to R2;

with the proviso that at least R_1 or R_2 is selected from the polypeptide of formula (I) , (II), or (III); and

said hematopoietic protein can optionally be immediately preceded by (methionine $^{-1}$), (alanine $^{-1}$) or (methionine $^{-2}$, alanine $^{-1}$).

[0021] The more preferred breakpoints at which new C-terminus and N-terminus can be made in the polypeptide (I) above are; 38-39, 39-40, 40-41, 41-42, 48-49, 53-54, 54-55, 55-56, 56-57, 57-58, 58-59, 59-60, 60-61, 61-62, 62-63, 64-65, 65-66, 66-67, 67-68, 68-69, 69-70, 96-97, 125-126, 126-127, 127-128, 128-129, 129-130, 130-131, 131-132, 132-133, 133-134, 134-135, 135-136, 136-137, 137-138, 138-139, 139-140, 140-141 and 141-142.

[0022] The most preferred breakpoints at which new C-terminus and N-terminus can be made in the polypeptide (I) above are; 38-39, 48-49, 96-97, 125-126, 132-133 and 141-142.

[0023] The more preferred breakpoints at which new Cterminus and N-terminus can be made in the polypeptide (II)
above are; 28-29, 29-30, 30-31, 31-32, 32-33, 33-34, 34-35,
35-36, 36-37, 37-38, 38-39, 39-40, 66-67, 67-68, 68-69, 69-70,
70-71, 84-85, 85-86, 86-87, 87-88, 88-89, 89-90, 90-91, 98-99,
99-100, 100-101 and 101-102.

[0024] The most preferred breakpoints at which new C-terminus and N-terminus can be made in the polypeptide (II) above are; 34-35, 69-70 and 90-91.

[0025] The more preferred breakpoints at which new C
5 terminus and N-terminus can be made in the polypeptide (III)

above or the amino acid sequence of (SEQ ID NO:256) are; 80
81, 81-82, 82-83, 83-84, 84-85, 85-86, 86-87, 108-109, 109
110, 110-111, 111-112, 112-113, 113-114, 114-115, 115-116,

116-117, 117-118, 118-119, 119-120, 120-121, 121-122, 122-123,

10 123-124, 124-125, 125-126 and 126-127.

[0026] The most preferred breakpoints at which new C-terminus and N-terminus can be made in the polypeptide (III) above or the amino acid sequence of (SEQ ID NO:256) are; 81-82, 108-109, 115-116, 119-120, 122-123 and 125-126.

15 [0027] The invention is also intended to include multifunctional receptor agoinist which comprises a sequence rearranged c-mpl receptor agonist in which the cysteine at position 7 and/or 151 are substituted with another amino acid. Preferably, the substitution at position 7 and 151 is Ser, 20 Ala, Gly, His, Asn, Asp, Thr, Phe or Thr. More preferably, the substitution at position 7 and 151 is Ser, Ala, Gly, His or Asn.

[0028] The multifunctional receptor agonist of the present invention can also be represented by the following formula:

$$(T^{1})_{a}-(L^{1})_{b}-X^{1}-(L)_{C}-X^{2}-(L^{2})_{d}-(T^{2})_{e}$$

$$X^{1}-(L)_{C}-X^{2}-(L)_{-Y^{1}-(L)_{C}-Y^{2}}$$

in which:

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 ${\rm X}^1$ is a peptide comprising an amino acid sequence corresponding to the sequence of residues n+1 through J of the original protein having amino acids residues numbered sequentially 1 through J with an amino terminus at residue 1;

L is an optional linker;

 ${\rm X}^2$ is a peptide comprising an amino acid sequence of residues 1 through n of the original protein;

Y¹ is a peptide comprising an amino acid sequence 15 corresponding to the sequence of residues n=1 through K of the original protein having amino acids residues numbered sequentially 1 through K with an amino terminus at residue 1;

 Y^2 is a peptide comprising an amino acid sequence of residues 1 through n of the original protein;

20 L^1 and L^2 are optional peptide spacers:

n is an integer ranging from 1 to J-1;

b, c, and d are each independently 0 or 1;

a and e are either 0 or 1, provided that both a and e cannot both be 0; and

25 T^1 and T^2 are proteins.

- [0029] Additionally, the present invention relates recombinant expression vectors comprising nucleotide sequences encoding the multi-functional hematopoietic receptor agonists, related microbial expression systems, and processes for making the multi-functional hematopoietic receptor agonists. The invention also relates to pharmaceutical compositions containing the multi-functional hematopoietic agonists, and methods for the multi-functional using hematopoietic receptor agonists.
- 10 [0030] In addition to the use of the multi-functional hematopoietic receptor agonists of the present invention in vivo, it is envisioned that in vitro uses would include the ability to stimulate bone marrow and blood cell activation and growth before infusion into patients.

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BRIEF DESCRIPTION OF THE FIGURES

[0031] Figure 1 schematically illustrates the sequence rearrangement of a protein. The N-terminus (N) and the C-terminus (C) of the native protein are joined through a linker, or joined directly. The protein is opened at a breakpoint creating a new N-terminus (new N) and a new C-terminus (new-C) resulting in a protein with a new linear amino acid sequence. A rearranged molecule may be synthesized de novo as linear molecule and not go through the steps of joining the original N-terminus and the C-terminus and opening of the protein at the breakpoint.

[0032] Figure 2 shows a schematic of Method I, for creating new proteins in which the original N-terminus and C-terminus of the native protein are joined with a linker and different N-terminus and C-terminus of the protein are created. In the example shown the sequence rearrangement results in a new gene encoding a protein with a new N-terminus created at amino acid 97 of the original protein, the original C-terminus (a.a. 174) joined to the amino acid 11 (a.a. 1- 10 are deleted) through a linker region and a new C-terminus created at amino acid 96 of the original sequence.

[0033] Figure 3 shows a schematic of Method II, for creating new proteins in which the original N-terminus and C-terminus of the native protein are joined without a linker and

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different N-terminus and C-terminus of the protein are created. In the example shown the sequence rearrangement results in a new gene encoding a protein with a new N-terminus created at amino acid 97 of the original protein, the original C-terminus (a.a. 174) joined to the original N-terminus and a new C-terminus created at amino acid 96 of the original sequence.

[0034] Figure 4 shows a schematic of Method III, for creating new proteins in which the original N-terminus and C-terminus of the native protein are joined with a linker and different N-terminus and C-terminus of the protein are created. In the example shown the sequence rearrangement results in a new gene encoding a protein with a new N-terminus created at amino acid 97 of the original protein, the original C-terminus (a.a. 174) joined to amino acid 1 through a linker region and a new C-terminus created at amino acid 96 of the original sequence.

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DETAILED DESCRIPTION OF THE INVENTION

The present invention encompasses multi-functional hematopoietic receptor agonists formed from covalently linked polypeptides, each of which may act through a different and specific cell receptor to initiate complementary biological activities. Hematopoiesis requires а complex series cellular events in which stem cells generate continuously into large populations of maturing cells in all major lineages. currently at least 20 known regulators with There are hematopoietic proliferative activity. Most οf these proliferative regulators can only stimulate one or another type of colony formation in vitro, the precise pattern of colony formation stimulated by each regulator is distinctive. No two regulators stimulate exactly the same pattern of colony formation, as evaluated by colony numbers or, more importantly, by the lineage and maturation pattern of the cells making up the developing colonies. Proliferative responses can most readily be analyzed in simplified in vitro culture systems. Three quite different parameters can be distinguished: alteration in colony size, alteration in colony numbers and cell lineage. Two or more factors may act on the progenitor cell, inducing the formation of larger number of progeny thereby increasing the colony size. Two or more factors may allow increased number of progenitor cells to

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proliferate either because distinct subsets of progenitors cells exist that respond exclusively to one factor or because some progenitors require stimulation by two or more factors additional before being able to respond. Activation of receptors on a cell by the use of two or more factors is likely to enhance the mitotic signal because of coalescence of initially differing signal pathways into a common final pathway reaching the nucleus (Metcalf, Nature 339:27, 1989). Other mechanisms could explain synergy. For example, if one signaling pathway is limited by an intermediate activation of an additional signaling pathway which is caused by a second factor, then this may result in a super additive response. In some cases, activation of one receptor type can induce an enhanced expression of other receptors (Metcalf, Blood 82:3515-3523, 1993). Two or more factors may result in a different pattern of cell lineages than from a single factor. The use of multi-functional hematopoietic receptor agonists may have a potential clinical advantage resulting from a proliferative response that is not possible by any single factor.

[0036] The receptors of hematopoietic and other growth factors can be grouped into two distinct families of related proteins: (1) tyrosine kinase receptors, including those for epidermal growth factor, M-CSF (Sherr, Blood 75:1, 1990) and

SCF (Yarden et al., EMBO J. **6**:3341, 1987): (2) hematopoietic receptors, not containing a tyrosine kinase domain, but exhibiting obvious homology in their extracellular domain (Bazan, PNAS USA 87:6934-6938, 1990). Included in this 5 latter group are erythropoietin (EPO) (D'Andrea et al., Cell 57:277, 1989), GM-CSF (Gearing et al., EMBO J. 8:3667, 1989), IL-3 (Kitamura et al., Cell 66:1165, 1991), G-CSF (Fukunaga et al., J. Bio. Chem. 265:14008-15, 1990), IL-4 (Harada et al., PNAS USA 87:857, 1990), IL-5 (Takaki et al., EMBO J. 9:4367, 10 1990), IL-6 (Yamasaki et al., Science 241:825, 1988), IL-7 (Goodwin et al., Cell 60:941-51, 1990), LIF (Gearing et al., EMBO J. 10:2839, 1991) and IL-2 (Cosman et al., Mol-Immunol. 23: 935-94, 1986). Most of the latter group of receptors exists in a high-affinity form as heterodimers. After ligand 15 binding, the specific a-chains become associated with at least one other receptor chain (b-chain, g-chain). Many of these factors share a common receptor subunit. The a-chains for GM-CSF, IL-3 and IL-5 share the same b-chain (Kitamura et al., Cell 66:1165, 1991), Takaki et al., EMBO J. 10:2833-8, 1991) 20 and receptor complexes for IL-6, LIF and IL-11 share a common b-chain (gp130) (Taga et al., Cell 58:573-81, 1989; Gearing et al., Science 255:1434-7, 1992). The receptor complexes of IL-2, IL-4, IL-7, IL-9 and IL-15 share a common g-chain (Kondo et al., Science 262:1874, 1993; Russell et al., Science 266:

1042-1045, 1993; Noguchi et al., *Science* **262**:1877, 1993; Giri et al., *EMBO J.* **13**:2822-2830, 1994).

[0037] The use of a multiply acting hematopoietic factor may also have a potential advantage by reducing the demands placed on factor-producing cells and their induction systems. If there are limitations in the ability of a cell to produce a factor, then by lowering the required concentrations of each of the factors, and using them in combination may usefully reduce demands on the factor-producing cells. The use of a multiply acting hematopoietic factor may lower the amount of the factors that would be needed, probably reducing the likelihood of adverse side-effects.

[0038] Novel compounds of this invention are represented by a formula selected from the group consisting of:

15 $R_1-L_1-R_2$, $R_2-L_1-R_1$, R_1-R_2 , and R_2-R_1

[0039] Where R₁ and R₂ are as defined above.

[0040] R2 is preferably a colony stimulating factor with a different but complementary activity than R1. By complementary activity is meant activity which enhances or changes the response to another cell modulator. The R1 polypeptide is joined either directly or through a linker segment to the R2 polypeptide. The term "directly" defines multi-functional hematopoietic receptor agonists in which the

polypeptides are joined without a peptide linker. Thus L_1 represents a chemical bond or polypeptide segment to which both R_1 and R_2 are joined in frame, most commonly L_1 is a linear peptide to which R_1 and R_2 are joined by amide bonds linking the carboxy terminus of R_1 to the amino terminus of L_1 and carboxy terminus of L_1 to the amino terminus of R_2 . By "joined in frame" is meant that there is no translation termination or disruption between the reading frames of the DNA encoding R_1 and R_2 .

10 [0041] A non-exclusive list of other growth factors, i.e. colony stimulating factors (CSFs), are cytokines, lymphokines, interleukins, or hematopoietic growth factors which can be joined to (I), (II) or (III) include GM-CSF, G-CSF, c-mpl ligand (also known as TPO or MGDF), M-CSF, erythropoietin 15 (EPO), IL-1, IL-4, IL-2, IL-3, IL-5, IL 6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, LIF, flt3 ligand, human growth hormone, and stem cell factor (SCF) also known as steel c-kit Additionally, this or ligand. invention encompasses the use of modified R1 or R2 molecules or mutated 20 or modified DNA sequences encoding these R1 or R2 molecules. also includes The present invention multi-functional hematopoietic receptor agonists in which R1 or R2 is an hIL-3 variant, c-mpl ligand variant, or G-CSF variant. A "hIL-3

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variant" is defined as a hIL-3 molecule which has amino acid substitutions and/or portions of hIL-3 deleted as disclosed in WO 94/12638, WO 94/12639 and WO 95/00646, as well as other variants known in the art. A "c-mpl ligand variant" is defined an c-mpl ligand molecule which has amino acid substitutions and/or portions of c-mpl ligand deleted, disclosed in United States Application Serial Number 08/383,035 as well as other variants known in the art. A "G-CSF variant" is defined an G-CSF molecule which has amino acid substitutions and/or portions of G-CSF deleted, as disclosed herein, as well as other variants known in the art.

[0042] The linking group (L1) is generally a polypeptide of between 1 and 500 amino acids in length. The linkers joining the two molecules are preferably designed to (1) allow the two molecules to fold and act independently of each other, (2) not propensity for developing an ordered structure which could interfere with the functional domains of the two proteins, (3) have minimal hydrophobic characteristics which could interact with the functional protein domains and (4) provide steric separation of R₁ and R₂ such that R₁ and R₂ simultaneously with could interact their receptors on a single cell. Typically surface amino acids in flexible protein regions include Gly, Asn and Ser. Virtually any permutation of amino acid sequences containing Gly, Asn

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and Ser would be expected to satisfy the above criteria for a linker sequence. Other neutral amino acids, such as Thr and Ala, may also be used in the linker sequence. Additional amino acids may also be included in the linkers due to the addition in the unique restriction sites linker sequence facilitate construction of the multi-functional hematopoietic receptor agonists.

[0043] Preferred L_1 linkers of the present invention include sequences selected from the group of formulas:

10 $(Gly^3Ser)^n$ (SEQ ID NO:4), $(Gly^4Ser)^n$ (SEQ ID NO:5), $(Gly^5Ser)^n$ (SEQ ID NO:6), $(Gly^nSer)^n$ (SEO ID NO:7) or $(AlaGlySer)^n$ (SEQ ID NO:8).

[0044] One example of a highly-flexible linker is the glycine and serine-rich spacer region present within the pIII protein of the filamentous bacteriophages, e.g. bacteriophages M13 or fd (Schaller et al., PNAS USA 72: 737-741, 1975). This region provides a long, flexible spacer region between two domains of the pIII surface protein. The spacer region 20 consists of the amino acid sequence:

> luGlyGlyGlySerGluGlyGlyGlySerGlyGlyGlyGlyGlyGl ySer (SEQ ID NO:9).

25 [0045] The present invention also includes linkers in which an endopeptidase recognition sequence is included. Such a cleavage site may be valuable to separate the individual

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components of the multi-functional hematopoietic receptor agonist to determine if they are properly folded and active in vitro. Examples of various endopeptidases include, but are not limited to, plasmin, enterokinase, kallikrein, urokinase, tissue plasminogen activator, clostripain, chymosin, collagenase, Russell's viper venom protease, postproline cleavage enzyme, V8 protease, Thrombin and factor Xa.

[0046] Peptide linker segments from the hinge region of heavy chain immunoglobulins IgG, IgA, IgM, IgD or IgE provide an angular relationship between the attached polypeptides. Especially useful are those hinge regions where the cysteines are replaced with serines. Preferred linkers of the present invention include sequences derived from murine IgG gamma 2b hinge region in which the cysteines have been changed to serines. These linkers may also include an endopeptidase cleavage site. Examples of such linkers include the following sequences:

IleSerGluProSerGlyProIleSerThrIleAsnProSerProProSerL
ys
GluSerHisLysSerPro (SEQ ID NO:10) and

IleGluGlyArgIleSerGluProSerGlyProIleSerThrIleAsnProSer
ProProSerLysGluSerHisLysSerPro (SEQ ID NO:11).

[0047] The present invention is, however, not limited by the form, size or number of linker sequences employed and the only requirement of the linker is that functionally it does

not interfere with the folding and function of the individual molecules of the multi-functional hematopoietic receptor agonist.

[0048] One aspect of the invention includes multifunctional hematopoietic receptor agonists which comprise a sequence rearranged c-mpl receptor agonist in which the cysteine(s) at position 7 and 151 of c-mpl ligand, have been substituted with another amino acid. Kaushansky et al. (Blood 86:255a Abstract 1008, 1995) teaches that all four of the 10 cysteines at positions 7, 29, 85, and 151 are required for bioactivity. The presence of cysteines in a protein can cause problems in processing when the protein is being produced recombinantly in a bacterial host. Microbially produced cysteine-containing proteins may tend to form multimers which 15 greatly complicate purification of the protein Several additional purification steps, such as reduction and reoxidation of the recombinant protein may be required to obtain the protein in the proper confirmation. Removal of one of the cysteine residues, with concurrent replacement by a 20 chemically equivalent neutral amino acid, would be desirable, in order to simplify the isolation and purification of the molecule. However, the successful removal of cysteines from biologically active molecules is unpredictable, in that the tertiary structure in the absence of the normally formed

disulfide bridges, can be substantially altered. A molecule in which a pair of cysteines at positions 7 and 151 are substituted with another amino acid may have one or more advantages including, but not limited to: 1) increased folding efficiency of the heterologously expressed protein; 2) elimination of mispaired disulfides, 3) use of milder refold conditions (ie. Guanidine vs. Urea); 4) increased purification yields, 5) increased protein solubility; and 6) increased protein stability.

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Determination of the Linker L2.

[0049] The length of the amino acid sequence of the linker L_2 to be used in R_1 and/or R_2 can be selected empirically or with guidance from structural information, or by using a combination of the two approaches.

[0050] When no structural information is available, a small series of linkers can be prepared for testing using a design whose length is varied in order to span a range from 0 to 50 Å and whose sequence is chosen in order to be consistent with surface exposure (hydrophilicity, Hopp & Woods, Mol. Immunol. 20: 483-489, 1983), Kyte & Doolittle, J. Mol. Biol. 157:105-132; solvent exposed surface area, Lee & Richards, J. Mol. Biol. 55:379-400, 1971) and the ability to adopt the necessary conformation with out deranging the conformation of R¹ or R²

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(conformationally flexible; Karplus & Schulz, Naturwissenschaften 72:212-213, 1985). Assuming an average of translation of 2.0 to 3.8 Å per residue, this would mean the length to test would be between 0 to 30 residues, with 0 to 15 residues being the preferred range. Exemplary of such an empirical series would be to construct linkers using cassette sequence such as Gly-Gly-Gly-Ser (SEQ ID NO:12) repeated n times, where n is 1, 2, 3 or 4. Those skilled in the art will recognize that there are many such sequences that vary in length or composition that can serve as linkers with primary consideration being that they be excessively long nor short (cf., Sandhu, Critical Biotech. 12: 437-462, 1992); if they are too long, entropy effects will likely destabilize the three-dimensional fold, and may also make folding kinetically impractical, and if they are too short, they will likely destabilize the molecule because of torsional or steric strain.

information will recognize that using the distance between the chain ends, defined as the distance between the c-alpha carbons, can be used to define the length of the sequence to be used, or at least to limit the number of possibilities that must be tested in an empirical selection of linkers. They will also recognize that it is sometimes the case that the

positions of the ends of the polypeptide chain are ill-defined in structural models derived from x-ray diffraction or nuclear magnetic resonance spectroscopy data, and that when true, this situation will therefore need to be taken into account in order to properly estimate the length of the linker required. From those residues whose positions are well defined are selected two residues that are close in sequence to the chain ends, and the distance between their c-alpha carbons is used to calculate an approximate length for a linker between them. 10 Using the calculated length as a guide, linkers with a range of number of residues (calculated using 2 to 3.8Å per residue) These linkers may be composed of the are then selected. original sequence, shortened or lengthened as necessary, and when lengthened the additional residues may be chosen to be 15 flexible and hydrophilic as described above; or optionally the original sequence may be substituted for using a series of linkers, one example being the Gly-Gly-Gly-Ser (SEQ ID NO:12) cassette approach mentioned above; or optionally a combination of the original sequence and new sequence having the 20 appropriate total length may be used.

Determination of the Amino and Carboxyl Termini of R₁ and R₂

[0052] Sequences of R₁ and R₂ capable of folding to 25 biologically active states can be prepared by appropriate

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selection of the beginning (amino terminus) and (carboxyl terminus) positions from within the polypeptide chain while using the linker sequence L2 described above. Amino and carboxyl termini are selected from within a common stretch of sequence, referred to as breakpoint region, using the guidelines described below. Α novel amino acid sequence is thus generated by selecting amino and carboxyl termini from within the same breakpoint region. In many cases the selection of the new termini will be such the original position of the carboxyl immediately preceded that of the amino terminus. those skilled in the art will recognize that selections of termini anywhere within the region may function, and that these will effectively lead to either deletions or additions to the amino or carboxyl portions of the new sequence.

[0053] It is a central tenet of molecular biology that the primary amino acid sequence of a protein dictates folding to the three-dimensional structure necessary for expression of its biological function. Methods are known to those skilled in the art to obtain and interpret three-dimensional structural information using x-ray diffraction of single protein crystals or nuclear magnetic resonance spectroscopy of protein solutions. Examples of structural information that are relevant to the identification of breakpoint regions

include the location and type of protein secondary structure (alpha and 3-10 helices, parallel and anti-parallel beta sheets, chain reversals and turns, and loops; Kabsch & Sander, Biopolymers 22: 2577-2637, 1983), the degree of solvent 5 exposure of amino acid residues, the extent and type of interactions of residues with one another (Chothia, Ann. Rev. and the static and dynamic **53**:537-572, 1984) Biochem. distribution of conformations along the polypeptide chain (Alber & Mathews, Methods Enzymol. 154: 511-533, 1987). 10 cases additional information is known about solvent exposure of residues; one example is a site of posttranslational attachment of carbohydrate which is necessarily on the surface of the protein. When experimental structural information is not available, or is not feasible to obtain, 15 methods are also available to analyze the primary amino acid sequence in order to make predictions of protein tertiary and secondary structure, solvent accessibility and the occurrence of turns and loops. Biochemical methods are also sometimes applicable for empirically determining surface exposure when 20 direct structural methods are not feasible; for example, using the identification of sites of chain scission following limited proteolysis in order to infer surface exposure (Gentile & Salvatore, Eur. J. Biochem. 218:603-621, 1993)

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either [0054] Thus using the experimentally structural information or predictive methods (e.g., Srinivisan & Rose Proteins: Struct., Funct. & Genetics, 22: 81-99, 1995) the parental amino acid sequence is inspected to classify regions according to whether or not they are integral to the maintenance of secondary and tertiary structure. The occurrence of sequences within regions that are known to be involved in periodic secondary structure (alpha and 3-10 helices, parallel and anti-parallel beta sheets) are regions that should be avoided. Similarly, regions of amino acid sequence that are observed or predicted to have a low degree of solvent exposure are more likely to be part of the socalled hydrophobic core of the protein and should also be avoided for selection of amino and carboxyl termini. In contrast, those regions that are known or predicted to be in surface turns or loops, and especially those regions that are known not to be required for biological activity, are the preferred sites for location of the extremes of the polypeptide chain. Continuous stretches of amino acid sequence that are preferred based on the above criteria are referred to as a breakpoint region.

Non-covalent Multifunctional Hematopoietic Growth Factors

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[0055] An alternative method for connecting two hematopoietic growth factors is by means of a non-covalent interaction. Such complexed proteins can be described by one of the formulae:

5 $R_1-C_1 + R_2-C_2$; or $C_1-R_1 + C_2-R_2$; $C_1-R_1 + R_2-C_2$; or $C_1-R_1 + R_2-C_2$.

[0056] R₁ and R₂ are as is defined above. Domains C1 and C2 are either identical or non-identical chemical structures, non-covalent, typically proteinaceous, which can form a specific association. Complexes between C1 and C2 result in a one-to-one stoichiometric relationship between R1 and R2 for Examples of domains which associate complex. "leucine zipper" domains of transcription factors, dimerization domains of bacterial transcription repressors and immunoglobulin constant domains. Covalent bonds link R1 and and R2 and C2, respectively. C1, As indicated in formulae, the domains C1 and C2 can be present either at the N-terminus or C-terminus of their corresponding hematopoietic growth factor (R). These multimerization domains (C1 and C2) include those derived from the bZIP family of proteins (Abel et al., Nature 341:24-25, 1989; Landshulz et al., Science 240:1759-1764, 1988; Pu et al., Nuc. Acid Res. 21:4348-4355, 1993; Kozarides et al., Nature 336:646-651, 1988), as well as multimerization domains of the helix-loop-helix family of

proteins (Abel et al., Nature 341:24-25, 1989; Murre et al., Cell 56:777-783, 1989; Tapscott et al., Science 242:405-411, Fisher et al., Genes & Dev. **5**:2342-2352, 1991). Preferred multi-functional hematopoietic receptor agonists of 5 the present invention include colony stimulating factors dimerized by virtue of their incorporation as translational multi-functional hematopoietic receptor agonists with the leucine dimerization domains of zipper the bZIP proteins Fos and Jun. The leucine zipper domain of Jun is 10 capable of interacting with identical domains. On the other hand, the leucine zipper domain of Fos interacts with the Jun leucine zipper domain, but does not interact with other Fos leucine zipper domains. Mixtures of Fos and Jun predominantly result in formation of Fos-Jun heterodimers. Consequently, 15 when joined to colony stimulating factors, the Jun domain can used to direct the formation of either heterodimers. Preferential formation of heterodimers can be achieved if one of the colony stimulating factor partners is engineered to possess the Jun leucine zipper domain while the 20 other is engineered to possess the Fos zipper.

[0057] Additional peptide sequences may also be added to facilitate purification or identification of multi-functional hematopoietic receptor agonist proteins (e.g., poly-His). A highly antigenic peptide may also be added that would enable

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rapid assay and facile purification of the multi-functional hematopoietic receptor agonist protein by a specific monoclonal antibody.

[0058] "Mutant amino acid sequence," "mutant protein", "variant protein", "mutein", or "mutant polypeptide" refers to a polypeptide having an amino acid sequence which varies from a native sequence due to amino acid deletions, substitutions, or both, or is encoded by a nucleotide sequence intentionally made variant from a native sequence.. "Native sequence" refers to an amino acid or nucleic acid sequence which is identical to a wild-type or native form of a gene or protein. Hematopoietic growth factors can be characterized by [0059] their ability to stimulate colony formation by hematopoietic progenitor cells. The colonies formed include erythroid, granulocyte, megakaryocyte, granulocytic macrophages and mixtures thereof. Many of the hematopoietic growth factors have demonstrated the ability to restore bone marrow function and peripheral blood cell populations to therapeutically beneficial levels in studies performed initially in primates and subsequently in humans. Many or all of these biological activities of hematopoietic growth factors

binding. Multi-functional hematopoietic receptor agonists of

the present invention may exhibit useful properties such as

signal transduction and high affinity receptor

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having similar or greater biological activity when compared to a single factor or by having improved half-life or decreased adverse side effects, or a combination of these properties.

[0060] Multi-functional hematopoietic receptor agonists which have little or no agonist activity maybe useful as antagonists, as antigens for the production of antibodies for use in immunology or immunotherapy, as genetic probes or as intermediates used to construct other useful hIL-3 muteins.

[0061] Biological activity of the multi-functional hematopoietic receptor agonist proteins of the present invention can be determined by DNA synthesis in factor-dependent cell lines or by counting the colony forming units in an in vitro bone marrow assay.

of the present invention may have an improved therapeutic profile as compared to single acting hematopoietic agonists. For example, some multi-functional hematopoietic receptor agonists of the present invention may have a similar or more potent growth factor activity relative to other hematopoietic agonists without having a similar or corresponding increase in side-effects.

[0063] The present invention also includes the DNA sequences which code for the multi-functional hematopoietic receptor agonist proteins, DNA sequences which are

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substantially similar and perform substantially the function, and DNA sequences which differ from the DNAs encoding the multi-functional hematopoietic receptor agonists of the invention only due to the degeneracy of the genetic code. Also included the present in invention are the oligonucleotide intermediates used to construct the mutant DNAs and the polypeptides coded for by these oligonucleotides.

[0064] Genetic engineering techniques now standard in the art (United States Patent 4,935,233 and Sambrook et al., "Molecular Cloning A Laboratory Manual", Cold Spring Harbor Laboratory, 1989) may be used in the construction of the DNA sequences of the present invention. One such method is cassette mutagenesis (Wells et al., Gene 34:315-323, 1985) in which a portion of the coding sequence in a plasmid is replaced with synthetic oligonucleotides that encode the desired amino acid substitutions in a portion of the gene between two restriction sites.

[0065] Pairs of complementary synthetic oligonucleotides encoding the desired gene can be made and annealed to each other. The DNA sequence of the oligonucleotide would encode sequence for amino acids of desired gene with the exception of those substituted and/or deleted from the sequence.

[0066] Plasmid DNA can be treated with the chosen restriction endonucleases then ligated to the annealed

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oligonucleotides. The ligated mixtures can be used competent JM101 cells to resistance transform to an appropriate antibiotic. Single colonies can be picked and the plasmid DNA examined by restriction analysis and/or DNA sequencing to identify plasmids with the desired genes.

[0067] Cloning of the DNA sequences of the novel multifunctional hematopoietic agonists wherein at least one of the with the DNA sequence of the other colony stimulating factor may be accomplished by the use of intermediate vectors. Alternatively one gene can be cloned directly into a vector containing the other gene. Linkers and adapters can be used

for joining the DNA sequences, as well as replacing lost sequences, where a restriction site was internal to the region of interest. Thus genetic material (DNA) encoding one polypeptide, peptide linker, and the other polypeptide is inserted into a suitable expression vector which is used to transform bacteria, yeast, insect cells or mammalian cells. The transformed organism is grown and the protein isolated by standard techniques. The resulting product is therefore a new protein which has a colony stimulating factor joined by a linker region to a second colony stimulating factor.

[0068] Another aspect of the present invention provides plasmid DNA vectors for use in the expression of these novel multi-functional hematopoietic receptor agonists. These

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vectors contain the novel DNA sequences described above which code for the novel polypeptides of the invention. Appropriate which can transform microorganisms capable expressing the multi-functional hematopoietic agonists include expression vectors comprising nucleotide sequences coding for the multi-functional hematopoietic receptor agonists joined to transcriptional and translational regulatory sequences which are selected according to the host cells used.

10 [0069] Vectors incorporating modified sequences as described above are included in the present invention and are useful in the production of the multi-functional hematopoietic receptor agonist polypeptides. The vector employed in the method also contains selected regulatory sequences in 15 operative association with the DNA coding sequences of the invention and which are capable of directing the replication and expression thereof in selected host cells.

[0070] As another aspect of the present invention, there is provided a method for producing the novel multi-functional hematopoietic receptor agonists. The method of the present invention involves culturing suitable cells or cell line, which has been transformed with a vector containing a DNA sequence coding for expression of a novel multi-functional hematopoietic receptor agonist. Suitable cells or cell lines

may be bacterial cells. For example, the various strains of coli are well-known as host cells in the field of biotechnology. Examples of such strains include E. coli strains JM101 (Yanish-Perron et al. *Gene* 33: 103-119, 1985) 5 MON105 (Obukowicz et al., Applied Environmental and Microbiology 58: 1511-1523, 1992). Also included in the present invention is the expression of the multi-functional hematopoietic receptor agonist protein utilizing a chromosomal expression vector for E. coli based on the bacteriophage Mu 10 (Weinberg et al., Gene 126: 25-33, 1993). Various strains of B. subtilis may also be employed in this method. Many strains of yeast cells known to those skilled in the art are also available as host cells for expression of the polypeptides of the present invention. When expressed in the E. coli 15 cytoplasm, the gene encoding the multi-functional hematopoietic receptor agonists of the present invention may also be constructed such that at the 5' end of the gene codons are added to encode Met -2 are -1 or Met -1 at the N-terminus of the protein. The N termini of proteins made in the cytoplasm 20 of E. coli are affected by post-translational processing by methionine aminopeptidase (Ben Bassat et al., J. Bac. 169:751-757, 1987) and possibly by other peptidases so that upon expression the methionine is cleaved off the N-terminus. The multi-functional hematopoietic receptor agonists of the

present invention may include multi-functional hematopoietic receptor agonist polypeptides having ${\rm Met}^{-1}$, ${\rm Ala}^{-1}$ or ${\rm Met}^{-2}$ - ${\rm Ala}^{-1}$ at the N-terminus. These mutant multi-functional hematopoietic receptor agonists may also be expressed in E. coli by fusing a secretion signal peptide to the N-terminus. This signal peptide is cleaved from the polypeptide as part of the secretion process.

Also suitable for use in the present invention are mammalian cells, such as Chinese hamster ovary cells (CHO). 10 General methods for expression of foreign genes in mammalian cells are reviewed in Kaufman, R. J., 1987) Genetic Engineering, Principles and Methods, Vol. 9, J. K. Setlow, editor, Plenum Press, New York. An expression vector is constructed in which a strong promoter capable of functioning 15 in mammalian cells drives transcription of a eukaryotic secretion signal peptide coding region, which translationally joined to the coding region for the multifunctional hematopoietic receptor agonist. For example, plasmids such as pcDNA I/Neo, pRc/RSV, and pRc/CMV (obtained 20 from Invitrogen Corp., San Diego, California) can be used. The eukaryotic secretion signal peptide coding region can be from the gene itself or it can be from another secreted mammalian protein (Bayne, M. L. et al., Proc. Natl. Acad. Sci.

USA 84: 2638-2642, 1987). After construction of the vector containing the gene, the vector DNA is transfected into mammalian cells. Such cells can be, for example, the COS7, HeLa, BHK, CHO, or mouse L lines. The cells can be cultured, for example, in DMEM media (JRH Scientific). The polypeptide 5 be recovered by standard into the media can biochemical approaches following transient expression for 24 hours after transfection of 72 the cells or after establishment of stable cell lines following selection for 10 antibiotic resistance. The selection of suitable mammalian cells and methods for transformation, culture, amplification, screening and product production purification are known in the art. See, e.g., Gething and Sambrook, Nature, 293:620-625, 1981), or alternatively, Kaufman et al, Mol. Cell. Biol., 5(7):1750-1759, 1985) or 15 Howley et al., U.S. Pat. No. 4,419,446. Another suitable mammalian cell line is the monkey COS-1 cell line. similarly useful mammalian cell line is the CV-1 cell line.

[0072] Where desired, insect cells may be utilized as host cells in the method of the present invention. See, e.g., Miller et al., Genetic Engineering, 8:277-298 (Plenum Press 1986) and references cited therein. In addition, general methods for expression of foreign genes in insect cells using Baculovirus vectors are described in: Summers, M. D. and

Smith, G. E., 1987) - A manual of methods for Baculovirus vectors and insect cell culture procedures, Texas Agricultural Experiment Station Bulletin No. 1555. An expression vector is constructed comprising a Baculovirus transfer vector, in which 5 strong Baculovirus promoter (such as the polyhedron promoter) drives transcription of a eukaryotic secretion signal peptide coding region, which is translationally joined to the coding region for the multi-functional hematopoietic receptor agonist polypeptide. For example, the plasmid 10 pVL1392 (obtained from Invitrogen Corp., San California) can be used. After construction of the vector carrying the gene encoding the multi-functional hematopoietic receptor agonist polypeptide, two micrograms of this DNA is co-transfected with one microgram of Baculovirus DNA 15 Summers & Smith, 1987) into insect cells, strain SF9. Pure Baculovirus recombinant carrying the multi-functional hematopoietic receptor agonist is used to infect cells cultured, for example, in Excell 401 serum-free medium (JRH Biosciences, Lenexa, Kansas). The multi-functional 20 hematopoietic receptor agonist secreted into the medium can be recovered by standard biochemical approaches. Supernatants from mammalian or insect cells expressing the multi-functional hematopoietic receptor agonist protein can be first

concentrated using any of a number of commercial concentration units.

[0073] The multi-functional hematopoietic receptor agonists of the present invention may be useful in the treatment of diseases characterized by decreased levels of either myeloid, 5 erythroid, lymphoid, or megakaryocyte cells hematopoietic system or combinations thereof. In addition, they may be used to activate mature myeloid and/or lymphoid Among conditions susceptible to treatment with the cells. 10 polypeptides of the present invention is leukopenia, reduction in the number of circulating leukocytes cells) in the peripheral blood. Leukopenia may be induced by exposure to certain viruses or to radiation. It is often a side effect of various forms of cancer therapy, e.g., exposure 15 chemotherapeutic drugs, radiation and of infection or Therapeutic treatment of leukopenia with these multi-functional hematopoietic receptor agonists of present invention may avoid undesirable side effects caused by treatment with presently available drugs.

20 [0074] The multi-functional hematopoietic receptor agonists of the present invention may be useful in the treatment of neutropenia and, for example, in the treatment of such conditions as aplastic anemia, cyclic neutropenia, idiopathic neutropenia, Chediak-Higashi syndrome, systemic lupus

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erythematosus (SLE), leukemia, myelodysplastic syndrome and myelofibrosis.

[0075] The multi-functional hematopoietic receptor agonist of the present invention may be useful in the treatment or prevention of thrombocytopenia. Currently the only therapy for thrombocytopenia is platelet transfusion which are costly and carry the significant risks of infection (HIV, alloimmunization. The multi-functional hematopoietic receptor agonist may alleviate or diminish the need for platelet transfusion. Severe thrombocytopenia may result from genetic defects such as Fanconi's Anemia, Wiscott-Aldrich, or May Hegglin syndromes. Acquired thrombocytopenia may result from allo-antibodies in auto- or as Immune Thrombocytopenia Purpura, Systemic Lupus Erythromatosis, hemolytic anemia, or fetal maternal incompatibility. In addition, splenomegaly, disseminated intravascular coagulation, thrombocytopenic purpura, infection or prosthetic heart valves may result in thrombocytopenia. Severe thrombocytopenia may also result from chemotherapy and/or radiation therapy or cancer. Thrombocytopenia may also result from marrow invasion by carcinoma, lymphoma, leukemia or fibrosis.

[0076] The multi-functional hematopoietic receptor agonists of the present invention may be useful in the mobilization of hematopoietic progenitors and stem cells in peripheral blood.

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and

Peripheral blood derived progenitors have been shown to be in reconstituting patients in the effective setting autologous marrow transplantation. Hematopoietic factors including G-CSF and GM-CSF have been shown to enhance the number of circulating progenitors and stem cells in the peripheral blood. This has simplified the procedure for peripheral stem cell collection and dramatically decreased the cost of the procedure by decreasing the number of pheresis required. The multi-functional hematopoietic receptor agonist may be useful in mobilization of stem cells and further enhance the efficacy of peripheral stem cell transplantation.

The multi-functional hematopoietic receptor agonists of the present invention may also be useful in the ex vivo expansion of hematopoietic progenitors and stem cells. Colony stimulating factors (CSFs), such as hIL-3, have administered alone, co-administered with other CSFs, or in combination with bone marrow transplants subsequent to high dose chemotherapy to treat the neutropenia and thrombocytopenia which are often the result of such treatment. However the period of severe neutropenia and thrombocytopenia may not be totally eliminated. The myeloid lineage, which is comprised of monocytes (macrophages), granulocytes (including neutrophils) and megakaryocytes, is critical in preventing

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Neutropenia and thrombocytopenia may also be the result of disease, genetic disorders, drugs, toxins, radiation and many therapeutic treatments such as conventional oncology therapy.

[0078] Bone marrow transplants have been used to treat this patient population. However, several problems are associated with the use of bone marrow to reconstitute a compromised hematopoietic system including: 1) the number of stem cells in bone marrow, spleen, or peripheral blood is limited, 2) Graft Versus Host Disease, 3) graft rejection and 4) possible contamination with tumor cells. Stem cells make up a very small percentage of the nucleated cells in the bone marrow, spleen and peripheral blood. It is clear that a dose response exists such that a greater number of stem cells will enhance hematopoietic recovery. Therefore, the in vitro expansion of stem cells should enhance hematopoietic recovery and patient survival. Bone marrow from an allogeneic donor has been used to provide bone marrow for transplant. However, Graft Versus Host Disease and graft rejection limit bone marrow transplantation even in recipients with HLA-matched sibling donors. An alternative to allogeneic bone marrow transplants is autologous bone marrow transplants. In autologous bone marrow transplants, some of the patient's own marrow harvested prior to myeloablative therapy, e.g. high dose chemotherapy, and is transplanted back into the patient

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afterwards. Autologous transplants eliminate the risk of Graft Versus Host Disease and graft rejection. However, autologous bone marrow transplants still present problems in terms of the limited number of stems cells in the marrow and possible contamination with tumor cells. The limited number of stem cells may be overcome by ex-vivo expansion of the stem cells. In addition, stem cells can be specifically isolated, based on the presence of specific surface antigens such as CD34+ in order to decrease tumor cell contamination of the marrow graft.

[0079] The following patents contain further details on separating stem cells, CD34+ cells, culturing the cells with hematopoietic factors, the use of the cells for the treatment of patients with hematopoietic disorders and the use of hematopoietic factors for cell expansion and gene therapy.

5,061,620 relates to compositions comprising human hematopoietic stem cells provided by separating the stem cells from dedicated cells.

5,199,942 describes a method for autologous hematopoietic cell transplantation comprising: (1) obtaining hematopoietic progenitor cells from a patient; (2) ex-vivo expansion of cells with a growth factor selected from the group consisting of IL-3, flt3 ligand, c-kit ligand, GM-CSF, IL-1, GM-CSF/IL-3 fusion protein and combinations thereof; (3) administering

cellular preparation to a patient.

5,240,856 relates to a cell separator that includes an apparatus for automatically controlling the cell separation process.

5 WO 91/16116 describes devices and methods for selectively isolating and separating target cells from a mixture of cells.

WO 91/18972 describes methods for in vitro culturing of bone marrow, by incubating suspension of bone marrow cells, using a hollow fiber bioreactor.

10 WO 92/18615 relates to a process for maintaining and expanding bone marrow cells, in a culture medium containing specific mixtures of cytokines, for use in transplants.

WO 93/08268 describes a method for selectively expanding stem cells, comprising the steps of (a) separating CD34+ stem cells from other cells and (b) incubating the separated cells in a selective medium, such that the stem cells are selectively expanded.

WO 93/18136 describes a process for in vitro support of mammalian cells derived from peripheral blood.

20 WO 93/18648 relates to a composition comprising human neutrophil precursor cells with a high content of myeloblasts and promyelocytes for treating genetic or acquired neutropenia.

WO 94/08039 describes a method of enrichment for human

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hematopoietic stem cells by selection for cells which express c-kit protein.

WO 94/11493 describes a stem cell population that are CD34+ and small in size, which are isolated using a counterflow elutriation method.

WO 94/27698 relates to a method combining immunoaffinity separation and continuous flow centrifugal separation for the selective separation of a nucleated heterogeneous cell population from a heterogeneous cell mixture.

10 WO 94/25848 describes a cell separation apparatus for collection and manipulation of target cells.

[0080] The long term culturing of highly enriched CD34+ precursors of hematopoietic progenitor cells from human bone marrow in cultures containing IL-1a, IL-3, IL-6 or GM-CSF is discussed in Brandt et al *J. Clin. Invest.* 86:932-941, 1990).

One aspect of the present invention provides a method for selective ex-vivo expansion of stem cells. The term "stem cell" refers to the totipotent hematopoietic stem cells as well as early precursors and progenitor cells which can be isolated from bone marrow, spleen or peripheral blood. "expansion" refers to the differentiation proliferation of the cells. The present invention provides a method for selective ex-vivo expansion of stem comprising the steps of: (a) separating stem cells from other

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culturing said separated stem cells cells, (b) selective media which contains multi-functional hematopoietic receptor agonist protein(s) and (c) harvesting said stems cells. Stem cells, as well as committed progenitor cells destined to become neutrophils, erythrocytes, platelets, etc. may be distinguished from most other cells by the presence or absence of particular progenitor marker antigens, such as CD34, that are present on the surface of these cells and/or by morphological characteristics. The phenotype for a highly enriched human stem cell fraction is reported as CD34+, Thy-1+ and lin-, but it is to be understood that the present invention is not limited to the expansion of this stem cell population. The CD34+ enriched human stem cell fraction can be separated by a number of reported methods, including affinity columns or beads, magnetic beads or flow cytometry using antibodies directed to surface antigens such as the CD34+. Further, physical separation methods such as counterflow elutriation may be used to enrich hematopoietic progenitors. The CD34+ progenitors are heterogeneous, and may be divided into several sub-populations characterized by the presence or absence of co-expression of different lineage associated cell surface associated molecules. The most immature progenitor cells do not express any known lineage associated markers, such as HLA-DR or CD38, but they may express CD90(thy-1).

Other surface antigens such as CD33, CD38, CD41, CD71, HLA-DR or c-kit can also be used to selectively isolate hematopoietic progenitors. The separated cells can be incubated in selected medium in a culture flask, sterile bag or in hollow fibers.

5 Various colony stimulating factors may be utilized in order to selectively expand cells. Representative factors that have been utilized for ex-vivo expansion of bone marrow include, c-kit ligand, IL-3, G-CSF, GM-CSF, IL-1, IL-6, IL-11, flt-3 ligand or combinations thereof. The proliferation of the stem cells can be monitored by enumerating the number of stem cells and other cells, by standard techniques (e.g. hemacytometer, CFU, LTCIC) or by flow cytometry prior and subsequent to incubation.

[0082] Several methods for ex-vivo expansion of stem cells

15 have been reported utilizing a number of selection methods and expansion using various colony stimulating factors including c-kit ligand (Brandt et al., Blood 83:1507-1514 [1994], McKenna et al., Blood 86:3413-3420 [1995]), IL-3 (Brandt et al., Blood 83:1507-1514 [1994], Sato et al., Blood 82:3600-20 3609 [1993]), G-CSF (Sato et al., Blood 82:3600-3609 [1993]), IL-1 (Muench et al., Blood 81:3463-3473 [1993]), IL-6 (Sato et al., Blood 82:3600-3609 [1993]), IL-11 (Lemoli et al., Exp. Hem. 21:1668-1672 [1993], Sato et al., Blood 82:3600-3609 [1993]), flt-3

ligand (McKenna et al., Blood 86:3413 3420 [1995]) and/or combinations thereof (Brandt et al., Blood 83:1507 1514 [1994], Haylock et al., Blood 80:1405-1412 [1992], Koller et al., Biotechnology 11:358-363 [1993], (Lemoli et al., Exp. 5 Hem. 21:1668-1672 [1993]), McKenna et al., Blood 86:3413-3420 [1995], Muench et al., Blood 81:3463-3473 [1993], Patchen et al., Biotherapy 7:13-26 [1994], Sato et al., Blood 82:3600-3609 [1993], Smith et al., Exp. Hem. 21:870-877 [1993], Steen et al., Stem Cells 12:214-224 [1994], Tsujino et al., Exp. 10 Hem. **21**:1379-1386 [1993]). Among the individual colony stimulating factors, hIL-3 has been shown to be one of the most potent in expanding peripheral blood CD34+ cells (Sato et al., Blood 82:3600-3609 [1993], Kobayashi et al., Blood 73:1836-1841 [1989]). However, no single factor has been shown 15 to be as effective as the combination of multiple factors. The present invention provides methods for ex vivo expansion that utilize multi-functional hematopoietic receptor agonists that are more effective than a single factor alone.

[0083] Another aspect of the invention provides methods of sustaining and/or expanding hematopoietic precursor cells which includes inoculating the cells into a culture vessel which contains a culture medium that has been conditioned by exposure to a stromal cell line such as HS-5 (WO 96/02662, Roecklein and Torok-Strob, Blood 85:997-1105, 1995) that has

been supplemented with a multi-functional hematopoietic receptor agonist of the present invention.

Another projected clinical use of growth factors has been in the in vitro activation of hematopoietic progenitors 5 and stem cells for gene therapy. Due to the long life-span of hematopoietic progenitor cells and the distribution of their daughter cells throughout the entire body, hematopoietic progenitor cells are good candidates for ex vivo transfection. In order to have the gene of interest 10 incorporated into the genome of the hematopoietic progenitor or stem cell one needs to stimulate cell division and DNA replication. Hematopoietic stem cells cycle at a very low frequency which means that growth factors may be useful to promote gene transduction and thereby enhance the clinical 15 prospects for gene therapy. Potential applications of gene therapy (review Crystal, Science 270:404-410 [1995]) include; 1) the treatment of many congenital metabolic disorders and immunodeficiencies (Kay and Woo, Trends Genet. 10:253-257 [1994]), 2) neurological disorders (Friedmann, Trends Genet. 20 10:210-214 [1994]), 3) cancer (Culver and Blaese, Genet. 10:174-178 [1994]) and 4) infectious diseases (Gilboa and Smith, Trends Genet. 10:139-144 [1994]).

[0085] There are a variety of methods, known to those with skill in the art, for introducing genetic material into a host

- cell. A number of vectors, both viral and non-viral have been developed for transferring therapeutic genes into primary cells. Viral based vectors include; 1) replication deficient recombinant retrovirus (Boris-Lawrie and Temin, Curr. Opin. Genet. Dev. 3:102-109 [1993], Boris-Lawrie and Temin, Annal. New York Acad. Sci. 716:59-71 [1994], Miller, Current Top. Microbiol. Immunol. 158:1-24 [1992]) and replication-deficient recombinant adenovirus (Berkner, BioTechniques **6:**616-629 [1988], Berkner, Current Top. Microbiol. Immunol. 158:39-66 10 [1992], Brody and Crystal, Annal. New York Acad. Sci. 716:90-103 [1994]). Non-viral based vectors include protein/DNA complexes (Cristiano et al., PNAS USA. 90:2122-2126 [1993], Curiel et al., PNAS USA 88:8850-8854 [1991], Curiel, Annal. New York Acad. Sci. 716:36-58 [1994]), electroporation 15 liposome mediated delivery such as cationic liposomes (Farhood et al., Annal. New York Acad. Sci. 716:23-35 [1994]).
- [0086] The present invention provides an improvement to the existing methods of expanding hematopoietic cells, which new genetic material has been introduced, in that it provides 20 methods utilizing multi-functional hematopoietic receptor agonist proteins that have improved biological activity, including an activity not seen by any single colony stimulation factor.

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[0087] Many drugs may cause bone marrow suppression or hematopoietic deficiencies. Examples of such drugs are AZT, DDI, alkylating agents and anti-metabolites chemotherapy, antibiotics such as chloramphenicol, penicillin, gancyclovir, daunomycin and sulfa drugs, phenothiazones, tranquilizers such as meprobamate, analgesics such aminopyrine and dipyrone, anti-convulsants such as phenytoin or carbamazepine, antithyroids such as propylthiouracil and methimazole and diuretics. The multi-functional hematopoietic receptor agonists of the present invention may be useful in preventing or treating the bone marrow suppression hematopoietic deficiencies which often occur in patients treated with these drugs.

[0088] Hematopoietic deficiencies may also occur as a result of viral, microbial or parasitic infections and as a result of treatment for renal disease or renal failure, e.g., dialysis. The multi-functional hematopoietic receptor agonists of the present invention may be useful in treating such hematopoietic deficiencies.

20 [0089] The treatment of hematopoietic deficiency include administration of a pharmaceutical composition containing the multi-functional hematopoietic receptor agonists to a patient. The multi-functional hematopoietic receptor agonists of the present invention may also be useful

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for the activation and amplification of hematopoietic precursor cells by treating these cells in vitro with the multi-functional hematopoietic receptor agonist proteins of the present invention prior to injecting the cells into a patient.

[0090] Various immunodeficiencies, e.g., in T and/or B lymphocytes, or immune disorders, e.g., rheumatoid arthritis, may also be beneficially affected by treatment with the multifunctional hematopoietic receptor agonists of the present Immunodeficiencies may be the result of viral invention. infections, e.g., HTLVI, HTLVII, HTLVIII, severe exposure to radiation, cancer therapy or the result of other medical treatment. The multi-functional hematopoietic receptor agonists of the present invention may also be employed, alone or in combination with other colony stimulating factors, in the treatment of other blood cell deficiencies, including thrombocytopenia (platelet deficiency), or anemia. Other uses for these novel polypeptides are the in vivo and ex vivo treatment of patients recovering from bone marrow transplants, and in the development of monoclonal and polyclonal antibodies generated by standard methods for diagnostic or therapeutic use.

[0091] Other aspects of the present invention are methods and therapeutic compositions for treating the conditions

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Such referred to above. compositions comprise therapeutically effective amount of one or more of the multifunctional hematopoietic receptor agonists of the present invention in a mixture with a pharmaceutically acceptable carrier. This composition can be administered either parenterally, intravenously or subcutaneously. When administered, the therapeutic composition for use in this invention is preferably in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such a parenterally acceptable protein solution, having due regard to pH, isotonicity, stability and the like, is within the skill of the art.

[0092] The dosage regimen involved in a method for treating the above-described conditions will be determined by the attending physician considering various factors which modify the action of drugs, e.g., the condition, body weight, sex and diet of the patient, the severity of any infection, time of administration and other clinical factors. Generally, a daily regimen may be in the range of $0.2-150~\mu g/kg$ of multifunctional hematopoietic receptor agonist protein per kilogram of body weight. Dosages would be adjusted relative to the activity of a given multi-functional hematopoietic receptor agonist protein and it would not be unreasonable to note that dosage regimens may include doses as low as 0.1~microgram and

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as high as 1 milligram per kilogram of body weight per day. In addition, there may exist specific circumstances where dosages of multi-functional hematopoietic receptor agonist would be adjusted higher or lower than the range of 0.2 - 150 micrograms per kilogram of body weight. These include coadministration with other colony stimulating factors or IL-3 factors; co-administration or growth chemotherapeutic drugs and/or radiation; the use of glycosylated multi-functional hematopoietic receptor agonist protein; and various patient-related issues mentioned earlier in this section. As indicated above, the therapeutic method and compositions may also include co-administration with other A non-exclusive list of other appropriate human factors. colony stimulating factors (CSFs), cytokines, lymphokines, hematopoietic growth factors and interleukins simultaneous or serial co-administration with the polypeptides of the present invention includes GM-CSF, G-CSF, c-mpl ligand (also known as TPO or MGDF), M-CSF, erythropoietin (EPO), IL-1, IL-4, IL-2, IL-3, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, IL-16, LIF, flt3 ligand, and stem cell factor (SCF) also known as steel factor or c-kit ligand, or combinations thereof. The dosage recited above would be adjusted to compensate for such additional components in the therapeutic composition. Progress of the treated patient can be monitored by periodic assessment of the hematological profile, e.g., differential cell count and the like.

MATERIALS AND METHODS

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[0093] Unless noted otherwise, all specialty chemicals were obtained from Sigma, Co. (St. Louis, MO). Restriction endonucleases and T4 DNA ligase were obtained from New England Biolabs (Beverly, MA) or Boehringer Mannheim (Indianapolis, IN).

Transformation of E. coli strains

[0094] E. coli strains, such as DH5á™ (Life Technologies, Gaithersburg, MD) and TG1 (Amersham Corp., Arlington Heights, IL) are used for transformation of ligation reactions and are the source of plasmid DNA for transfecting mammalian cells. E. coli strains, such as JM101 (Yanisch-Perron, et al., Gene, 33: 103-119, 1985) and MON105 (Obukowicz, et al., Appl. and Envir. Micr., 58: 1511-1523, 1992) can be used for expressing the multi-functional hematopoietic receptor agonist of the present invention in the cytoplasm or periplasmic space.

MON105 ATCC#55204: F-, lambda-,IN(rrnD, rrE)1, rpoD+, rpoH358

- DH5á™: F-, phi80dlacZdeltaM15, delta(lacZYA-argF)U169, deoR, recA1, endA1, hsdR17(rk-,mk+), phoA, supE44lamda-, thi-1, gyrA96, relA1
- TG1: delta(lac-pro), supE, thi-1, hsdD5/F'(traD36, proA+B+, lacIq, lacZdeltaM15)

JM101 ATCC#33876: delta (pro lac), supE, thi,
F'(traD36, proA+B+, lacIq, lacZdeltaM15)

 $DH5\acute{a}^{m}$ Subcloning efficiency cells are purchased as [0095] 5 competent cells and are ready for transformation using the manufacturer's protocol, while both E. coli strains TG1 and MON105 are rendered competent to take up DNA using a CaCl2 Typically, 20 to 50 mL of cells are grown in LB method. medium (1% bacto-tryptone, 0.5% bacto-yeast extract, 150 mM 10 NaCl) to a density of approximately 1.0 optical density unit at 600 nanometers (OD600) as measured by a Baush & Lomb Spectronic spectrophotometer (Rochester, NY). The cells are collected by centrifugation and resuspended in one-fifth culture volume of CaCl2 solution (50 mM CaCl2, 10 mM Tris-Cl, 15 pH7.4) and are held at 4°C for 30 minutes. The cells are again collected by centrifugation and resuspended in one-tenth culture volume of CaCl₂ solution. Ligated DNA is added to 0.2 mL of these cells, and the samples are held at 4°C for 30-60The samples are shifted to 42°C for two minutes and 20 1.0 mL of LB is added prior to shaking the samples at 37°C for one hour. Cells from these samples are spread on plates (LB medium plus 1.5% bacto-agar) containing either ampicillin (100 micrograms/mL, ug/mL) when selecting for ampicillin-resistant transformants, or spectinomycin (75 ug/mL) when selecting for 25 spectinomycin-resistant transformants. The plates are

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incubated overnight at 37°C. Colonies are picked and inoculated into LB plus appropriate antibiotic (100 ug/mL ampicillin or 75 ug/mL spectinomycin) and are grown at 37°C while shaking.

Methods For Creation of Genes
With New N-Terminus/C-Terminus

Method I.

Creation of genes with new N-terminus/C-terminus which contain a linker region (L2).

[0096] Genes with new N-terminus/C-terminus which contain a linker region (L₂) separating the original C-terminus and N-terminus can be made essentially following the method described in L. S. Mullins, et al J. Am. Chem. Soc. 116, 5529-5533, 1994). Multiple steps of polymerase chain reaction (PCR) amplifications are used to rearrange the DNA sequence encoding the primary amino acid sequence of the protein. The steps are illustrated in Figure 2.

[0097] In the first step, the first primer set ("new start" and "linker start") is used to create and amplify, from the original gene sequence, the DNA fragment ("Fragment Start") that contains the sequence encoding the new N-terminal portion of the new protein followed by the linker (L2) that connects the C-terminal and N-terminal ends of the original protein. In the second step, the second primer set ("new stop" and "linker stop") is used to create and amplify, from the original gene

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sequence, the DNA fragment ("Fragment Stop") that encodes the same linker as used above, followed by the new C-terminal portion of the new protein. The "new start" and "new stop" primers are designed to include the appropriate restriction sites which allow cloning of the new gene into expression plasmids. Typical PCR conditions are one cycle 95°C melting for two minutes; 25 cycles 94°C denaturation for one minute, 50°C annealing for one minute and 72°C extension for one minute; plus one cycle 72°C extension for seven minutes. A Perkin Elmer GeneAmp PCR Core Reagents kit is used. A 100 ul reaction contains 100 pmole of each primer and one ug of template DNA; and 1x PCR buffer, 200 uM dGTP, 200 uM dATP, 200 uM dTTP, 200 uM dCTP, 2.5 units AmpliTaq DNA polymerase and 2 mM MgCl2. PCR reactions are performed in a Model 480 DNA thermal cycler (Perkin Elmer Corporation, Norwalk, CT).

[0098] "Fragment Start" and "Fragment Stop", which have complementary sequence in the linker region and the coding sequence for the two amino acids on both sides of the linker, are joined together in a third PCR step to make the full-length gene encoding the new protein. The DNA fragments "Fragment Start" and "Fragment Stop" are resolved on a 1% TAE gel, stained with ethidium bromide and isolated using a Qiaex Gel Extraction kit (Qiagen). These fragments are combined in equimolar quantities, heated at 70°C for ten minutes and slow

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cooled to allow annealing through their shared sequence in "linker start" and "linker stop". In the third PCR step, primers "new start" and "new stop" are added to the annealed fragments to create and amplify the full-length new Nterminus/C-terminus gene. Typical PCR conditions are one 95°C cvcle melting for two minutes; 25 cycles 94°C denaturation for one minute, 60°C annealing for one minute and 72°C extension for one minute; plus one cycle 72°C extension for seven minutes. A Perkin Elmer GeneAmp PCR Core Reagents kit is used. A 100 ul reaction contains 100 pmole of each primer and approximately 0.5 ug of DNA; and 1x PCR buffer, 200 uM dGTP, 200 uM dATP, 200 uM dTTP, 200 uM dCTP, 2.5 units AmpliTaq DNA polymerase and 2 mM MgCl2. PCR reactions are purified using a Wizard PCR Preps kit (Promega).

Method II.
Creation of genes with new

N-terminus/C-terminus without a linker region.

[0099] New N-terminus/C-terminus genes without a linker joining the original N-terminus and C-terminus can be made using two steps of PCR amplification and a blunt end ligation. The steps are illustrated in Figure 3. In the first step, the primer set ("new start" and "P-bl start") is used to create and amplify, from the original gene sequence, the DNA fragment ("Fragment Start") that contains the sequence encoding the new N-terminal portion of the new protein. In the second step,

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the primer set ("new stop" and "P-bl stop") is used to create and amplify, from gene sequence, the DNA fragment ("Fragment Stop") that contains the sequence encoding the new C-terminal portion of the new protein. The "new start" and "new stop" primers are designed to include appropriate restriction sites which allow cloning of the new gene into expression vectors. Typical PCR conditions are one cycle 95°C melting for two minutes; 25 cycles 94°C denaturation for one minute, 50°C annealing for 45 seconds and 72°C extension for 45 seconds. Deep Vent polymerase (New England Biolabs) is used to reduce the occurrence of overhangs in conditions recommended by the manufacturer. The "P-bl start" and "P-bl stop" primers are phosphorylated at the 5' end to aid in the subsequent blunt end ligation of "Fragment Start" and "Fragment Stop" to each 15 other. A 100 ul reaction contained 150 pmole of each primer and one ug of template DNA; and 1x Vent buffer (New England Biolabs), 300 uM dGTP, 300 uM dATP, 300 uM dTTP, 300 uM dCTP, and 1 unit Deep Vent polymerase. PCR reactions are performed in a Model 480 DNA thermal cycler (Perkin Elmer Corporation, Norwalk, CT). PCR reaction products are purified using a Wizard PCR Preps kit (Promega).

[00100] The primers are designed to include appropriate restriction sites which allow for the cloning of the new gene into expression vectors. Typically "Fragment Start"

designed to create NcoI restriction site , and "Fragment Stop" is designed to create a HindIII restriction site. Restriction digest reactions are purified using a Magic DNA Clean-up System kit (Promega). Fragments Start and Stop are resolved on a 1% TAE gel, stained with ethidium bromide and isolated 5 using a Qiaex Gel Extraction kit (Qiagen). These fragments are combined with and annealed to the ends of the ~ 3800 base pair NcoI/HindIII vector fragment of pMON3934 by heating at 50°C for ten minutes and allowed to slow cool. The three 10 fragments are ligated together using T4 DNA ligase (Boehringer Mannheim). The result is a plasmid containing the full-length new N-terminus/C-terminus gene. A portion of the ligation reaction is used to transform E. coli strain DH5á cells (Life Technologies, Gaithersburg, MD). Plasmid DNA is purified and 15 sequence confirmed as below.

Method III. Creation of new N-terminus/C-terminus genes by tandem-duplication method

20 [0100] New N-terminus/C-terminus genes can be made based on the method described in R. A. Horlick, et al Protein Eng. **5**:427-431, 1992). Polymerase chain reaction (PCR) amplification of the new N-terminus/C-terminus performed using a tandemly duplicated template DNA. The steps 25 are illustrated in Figure 3.

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[0101] The tandemly-duplicated template DNA is created by cloning and contains two copies of the gene separated by DNA sequence encoding a linker connecting the original C- and Nterminal ends of the two copies of the gene. Specific primer sets are used to create and amplify a full-length new N terminus/C-terminus gene from the tandemly-duplicated template These primers are designed to include appropriate restriction sites which allow for the cloning of the new gene into expression vectors. Typical PCR conditions are one cycle 95°C melting for two minutes; 25 cycles 94°C denaturation for one minute, 50°C annealing for one minute and 72°C extension for one minute; plus one cycle 72°C extension for seven A Perkin Elmer GeneAmp PCR Core Reagents kit (Perkin minutes. Elmer Corporation, Norwalk, CT) is used. A 100 ul reaction contains 100 pmole of each primer and one ug of template DNA; and 1x PCR buffer, 200 uM dGTP, 200 uM dATP, 200 uM dTTP, 200 uM dCTP, 2.5 units AmpliTaq DNA polymerase and 2 mM MqCl₂. PCR reactions are performed in a Model 480 DNA thermal cycler (Perkin Elmer Corporation, Norwalk, CT). PCR reactions are purified using a Wizard PCR Preps kit (Promega).

Cloning of new N-terminus/C-terminus genes into multi-functional receptor agonist expression vectors.

[0102] The new N-terminus/C-terminus gene is digested with restriction endonucleases to create ends that are compatible

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to insertion into an expression vector containing another colony stimulating factor gene. This expression vector is likewise digested with restriction endonucleases to form compatible ends. After purification, the gene and the vector DNAs are combined and ligated using T4 DNA ligase. A portion of the ligation reaction is used to transform E. coli. Plasmid DNA is purified and sequenced to confirm the correct insert. The correct clones are grown for protein expression.

DNA isolation and characterization

[0103] Plasmid DNA can be isolated by a number of different methods and using commercially available kits known to those skilled in the art. A few such methods are shown herein. Plasmid DNA is isolated using the Promega Wizard™ Miniprep kit (Madison, WI), the Qiagen QIAwell Plasmid isolation kits (Chatsworth, CA) or Qiagen Plasmid Midi kit. These kits follow the same general procedure for plasmid DNA isolation. Briefly, cells are pelleted by centrifugation (5000 x g), plasmid DNA released with sequential NaOH/acid treatment, and cellular debris is removed by centrifugation (10000 x g). The supernatant (containing the plasmid DNA) is loaded onto a column containing a DNA-binding resin, the column is washed, and plasmid DNA eluted with TE. After screening for the colonies with the plasmid of interest, the E. coli cells are inoculated into 50-100 mls of LB plus appropriate antibiotic

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for overnight growth at 37°C in an air incubator while shaking. The purified plasmid DNA is used for DNA sequencing, further restriction enzyme digestion, additional subcloning of DNA fragments and transfection into mammalian, *E. coli* or other cells.

Sequence confirmation.

[0104] Purified plasmid is resuspended DNA in dH₂O and quantitated by measuring the absorbance at 260/280 nm in a Bausch and Lomb Spectronic 601 UV spectrometer. DNA samples are sequenced using ABI PRISM™ DyeDeoxy™ terminator sequencing chemistry (Applied Biosystems Division of Perkin Corporation, Lincoln City, CA) kits (Part Number 401388 or 402078) according to the manufacturers suggested protocol usually modified by the addition of 5% DMSO to the sequencing Sequencing reactions are performed in a Model 480 DNA thermal cycler (Perkin Elmer Corporation, Norwalk, CT) following the recommended amplification conditions. Samples are purified to remove excess dye terminators with Centri-Sep™ spin columns (Princeton Separations, Adelphia, NJ) lyophilized. Fluorescent dye labeled sequencing reactions are resuspended in deionized formamide, and sequenced denaturing 4.75% polyacrylamide-8M urea gels using an ABI Model 373A automated DNA sequencer. Overlapping DNA sequence fragments are analyzed and assembled into master DNA contigs using Sequencher v2.1 DNA analysis software (Gene Codes Corporation, Ann Arbor, MI).

Expression of multi-functional receptor agonists in mammalian cells

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Mammalian Cell Transfection/Production of Conditioned Media [0105] The BHK-21 cell line can be obtained from the ATCC (Rockville, MD). The cells are cultured in Dulbecco's modified Eagle media (DMEM/high-glucose), supplemented to 2 mM (mM) Lglutamine and 10% fetal bovine serum (FBS). This formulation is designated BHK growth media. Selective media is BHK growth media supplemented with 453 units/mL hygromycin B (Calbiochem, San Diego, CA). The BHK-21 cell line was previously stably transfected with the HSV transactivating protein VP16, which transactivates the IE110 promoter found on the plasmid pMON3359 (See Hippenmeyer et al., Bio/Technology, pp.1037-1041, 1993). The VP16 protein drives expression of genes inserted behind the IE110 promoter. BHK-21 cells expressing the transactivating protein VP16 are designated BHK-VP16. The plasmid pMON1118 (See Highkin et al., Poultry Sci., 70: 970-981, 1991) expresses the hygromycin resistance gene from the SV40 promoter. A similar plasmid is available from ATCC, pSV2hph.

25 [0106] BHK-VP16 cells are seeded into a 60 millimeter (mm) tissue culture dish at 3 \times 10⁵ cells per dish 24 hours prior

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to transfection. Cells are transfected for 16 hours in 3 mL of "OPTIMEM"™ (Gibco-BRL, Gaithersburg, MD) containing 10 ug of plasmid DNA containing the gene of interest, 3 ug hygromycin resistance plasmid, pMON1118, and 80 uq οf Gibco-BRL "LIPOFECTAMINE"™ per dish. The media is subsequently aspirated and replaced with 3 mL of growth media. At 48 hours posttransfection, media from each dish is collected and assayed for activity (transient conditioned media). The cells are removed from the dish by trypsin-EDTA, diluted 1:10 and transferred to 100 mm tissue culture dishes containing 10 mL of selective media. After approximately 7 days in selective media, resistant cells grow into colonies several millimeters in diameter. The colonies are removed from the dish with filter paper (cut to approximately the same size as the colonies and soaked in trypsin/EDTA) and transferred individual wells of a 24 well plate containing 1 mL of selective media. After the clones are grown to confluence, the conditioned media is re-assayed, and positive clones expanded into growth media.

20 Expression of multi-functional receptor agonists in *E. coli*

[0107] E. coli strain MON105 or JM101 harboring the plasmid of interest are grown at 37°C in M9 plus casamino acids medium with shaking in a air incubator Model G25 from New Brunswick

Scientific (Edison, New Jersey). Growth is monitored at OD600 until it reaches a value of 1.0 at which time Nalidixic acid milligrams/mL) in 0.1 N NaOH is added to a final concentration of 50 µg/mL. The cultures are then shaken at 37°C for three to four additional hours. A high degree of aeration is maintained throughout culture period in order to achieve maximal production of the desired gene product. cells are examined under a light microscope for the presence of inclusion bodies (IB). One mL aliquots of the culture are removed for analysis of protein content by boiling the pelleted cells, treating them with reducing buffer electrophoresis via SDS-PAGE (see Maniatis et al. Molecular Cloning: Α Laboratory Manual, 1982). The culture is centrifuged ($5000 \times g$) to pellet the cells.

Inclusion Body preparation, Extraction, Refolding, Dialysis, DEAE Chromatography, and Characterization of the multi-functional hematopoietic receptor agonists which accumulate as inclusion bodies in E. coli.

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Isolation of Inclusion Bodies:

[0108] The cell pellet from a 330 mL *E. coli* culture is resuspended in 15 mL of sonication buffer (10 mM 2-amino-2-(hydroxymethyl) 1,3-propanediol hydrochloride (Tris-HCl), pH 8.0 + 1 mM ethylenediaminetetraacetic acid (EDTA). These resuspended cells are sonicated using the microtip probe of a Sonicator Cell Disruptor (Model W-375, Heat Systems-

Ultrasonics, Inc., Farmingdale, New York). Three rounds of sonication in sonication buffer followed by centrifugation are employed to disrupt the cells and wash the inclusion bodies (IB). The first round of sonication is a 3 minute burst followed by a 1 minute burst, and the final two rounds of sonication are for 1 minute each.

Extraction and refolding of proteins from inclusion body pellets:

- 10 [0109] Following the final centrifugation step, the IB pellet is resuspended in 10 mL of 50 mM Tris-HCl, pH 9.5, 8 M urea and 5 mM dithiothreitol (DTT) and stirred at room temperature for approximately 45 minutes to allow for denaturation of the expressed protein.
- [0110] The extraction solution is transferred to a beaker containing 70 mL of 5 mM Tris-HCl, pH 9.5 and 2.3 M urea and gently stirred while exposed to air at 4°C for 18 to 48 hours to allow the proteins to refold. Refolding is monitored by analysis on a Vydac (Hesperia, Ca.) C18 reversed phase high pressure liquid chromatography (RP-HPLC) column (0.46x25 cm). A linear gradient of 40% to 65% acetonitrile, containing 0.1% trifluoroacetic acid (TFA), is employed to monitor the refold. This gradient is developed over 30 minutes at a flow rate of 1.5 mL per minute. Denatured proteins generally elute later in the gradient than the refolded proteins.

Purification

- [0111] Following the refold, contaminating $E.\ coli$ proteins are removed by acid precipitation. The pH of the refold solution is titrated to between pH 5.0 and pH 5.2 using 15% (v/v) acetic acid (HOAc). This solution is stirred at 4°C for 2 hours and then centrifuged for 20 minutes at 12,000 x g to pellet any insoluble protein.
- [0112] The supernatant from the acid precipitation step is 10 dialyzed using a Spectra/Por 3 membrane with a molecular weight cut off (MWCO) of 3,500 daltons. The dialysis is against 2 changes of 4 liters (a 50-fold excess) of 10 mM Tris-HCl, pH 8.0 for a total of 18 hours. Dialysis lowers the sample conductivity and removes urea prior to DEAE 15 chromatography. The sample is then centrifuged (20 minutes at 12,000 x g) to pellet any insoluble protein following dialysis.
- [0113] A Bio-Rad Bio-Scale DEAE2 column (7 x 52 mm) is used for ion exchange chromatography. The column is equilibrated in a buffer containing 10 mM Tris-HCl, pH 8.0, and a 0-to-500 mM sodium chloride (NaCl) gradient, in equilibration buffer, over 45 column volumes is used to elute the protein. A flow rate of 1.0 mL per minute is used throughout the run. Column fractions (2.0 mL per fraction) are collected across the gradient and analyzed by RP HPLC on a Vydac (Hesperia, Ca.)

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C18 column (0.46 x 25 cm). A linear gradient of 40% to 65% acetonitrile, containing 0.1% trifluoroacetic acid (TFA), is employed. This gradient is developed over 30 minutes at a flow rate of 1.5 mL per minute. Pooled fractions are then dialyzed against 2 changes of 4 liters (50-to-500-fold excess) of 10 mM ammonium acetate (NH4Ac), pH 4.0 for a total of 18 hours. Dialysis is performed using a Spectra/Por 3 membrane with a MWCO of 3,500 daltons. Finally, the sample is sterile filtered using a 0.22µm syringe filter (µStar LB syringe filter, Costar, Cambridge, Ma.), and stored at 4°C.

[0114] In some cases the folded proteins can be affinity purified using affinity reagents such as mAbs or receptor subunits attached to a suitable matrix. Alternatively, (or in addition) purification can be accomplished using any of a variety of chromatographic methods such as: ion exchange, gel filtration or hydrophobic chromatography or reversed phase HPLC.

[0115] These and other protein purification methods are described in detail in Methods in Enzymology, Volume 182 'Guide to Protein Purification' edited by Murray Deutscher, Academic Press, San Diego, CA (1990).

Protein Characterization:

[0116] The purified protein is analyzed by RP-HPLC, electrospray mass spectrometry, and SDS-PAGE. The protein

quantitation is done by amino acid composition, RP-HPLC, and Bradford protein determination. In some cases tryptic peptide mapping is performed in conjunction with electrospray mass spectrometry to confirm the identity of the protein.

5 AML Proliferation Assay for Bioactive Human Interleukin-3

[0117] The factor-dependent cell line AML 193 was obtained from the American Type Culture Collection (ATCC, Rockville, 10 This cell line, established from a patient with acute myelogenous leukemia, is a growth factor dependent cell line which displayed enhanced growth in GM-CSF supplemented medium (Lange, B., et al., Blood 70: 192, 1987; Valtieri, M., et al., J. Immunol. 138:4042, 1987). The ability of AML 193 cells to 15 proliferate in the presence of human IL-3 has also documented. (Santoli, D., et al., J. Immunol. 139: 1987). A cell line variant was used, AML 193 1.3, which was adapted for long term growth in IL-3 by washing out the growth factors and starving the cytokine dependent AML 193 cells for 20 growth factors for 24 hours. The cells are then replated at 1×10^5 cells/well in a 24 well plate in media containing 100 U/mL IL-3. It took approximately 2 months for the cells to grow rapidly in IL-3. These cells are maintained as AML 193 thereafter by supplementing tissue culture medium (see 25 below) with human IL-3.

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[0118] AML 193 1.3 cells are washed 6 times in cold Hanks balanced salt solution (HBSS, Gibco, Grand Island, NY) by centrifuging cell suspensions at 250 x g for 10 minutes followed by decantation of the supernatant. Pelleted cells are resuspended in HBSS and the procedure is repeated until six wash cycles are completed. Cells washed six times by this procedure are resuspended in tissue culture medium at a density ranging from 2 x 10^5 to 5 x 10^5 viable cells/mL. medium is prepared by supplementing Iscove's modified Dulbecco's Medium (IMDM, Hazelton, Lenexa, KS) with albumin, transferrin, lipids and 2-mercaptoethanol. Bovine albumin (Boehringer-Mannheim, Indianapolis, IN) is added at 500 µg/mL; human transferrin (Boehringer-Mannheim, Indianapolis, IN) is added 100 μq/mL; at soybean lipid (Boehringer-Mannheim, Indianapolis, IN) is added at 50 µg/mL; and 2-mercaptoethanol (Sigma, St. Louis, MO) is added at $5 \times 10^{-5} M$.

[0119] Serial dilutions of human interleukin-3 or multifunctional hematopoietic receptor agonist proteins are made in triplicate series in tissue culture medium supplemented as stated above in 96 well Costar 3596 tissue culture plates. Each well contained 50 µl of medium containing interleukin-3 or multi-functional hematopoietic receptor agonist proteins once serial dilutions are completed. Control wells contained tissue culture medium alone (negative control). AML 193 1.3

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cell suspensions prepared as above are added to each well by pipetting 50 μ l (2.5 x 10⁴ cells) into each well. culture plates are incubated at 37°C with 5% CO2 in humidified air for 3 days. On day 3, 0.5 μ Ci ³H-thymidine (2 Ci/mM, New England Nuclear, Boston, MA) is added in 50 µl of tissue culture medium. Cultures are incubated at 37°C with 5% CO2 in humidified air for 18-24 hours. Cellular DNA is harvested onto glass filter mats (Pharmacia LKB, Gaithersburg, MD) using a TOMTEC cell harvester (TOMTEC, Orange, CT) which utilized a water wash cycle followed by a 70% ethanol wash cycle. Filter mats are allowed to air dry and then placed into sample bags to which scintillation fluid (Scintiverse II, Scientific, St. Louis, MO or BetaPlate Scintillation Fluid, Pharmacia LKB, Gaithersburg, MD) is added. Beta emissions of samples from individual tissue culture wells are counted in a LKB BetaPlate model 1205 scintillation counter (Pharmacia LKB, Gaithersburg, MD) and data is expressed as counts per minute ³H-thymidine incorporated into cells from each tissue culture well. Activity of each human interleukin-3 preparation or multi-functional hematopoietic receptor agonist protein preparation is quantitated by measuring cell proliferation (3H-thymidine incorporation) induced by graded concentrations of interleukin-3 or multi-functional hematopoietic receptor agonist. Typically, concentration

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ranges from $0.05 \text{ pM} - 10^5 \text{ pM}$ are quantitated in these assays. Activity is determined by measuring the dose of interleukin-3 or multi-functional hematopoietic receptor agonist protein which provides 50% of maximal proliferation (EC50 = $0.5 \times$ 5 (maximum per 3H-thvmidine average counts minute of incorporated per well among triplicate cultures of all concentrations of interleukin-3 tested background proliferation measured by ³H-thymidine incorporation observed in triplicate cultures lacking interleukin-3). This EC50 10 value is also equivalent to 1 unit of bioactivity. assay is performed with native interleukin-3 as a reference standard so that relative activity levels could be assigned.

[0120] Typically, the multi-functional hematopoietic receptor agonist proteins were tested in a concentration range of 2000 pM to 0.06 pM titrated in serial 2 fold dilutions.

[0121] Activity for each sample was determined by the concentration which gave 50% of the maximal response by fitting a four-parameter logistic model to the data. It was observed that the upper plateau (maximal response) for the sample and the standard with which it was compared did not differ. Therefore relative potency calculation for each sample was determined from EC50 estimations for the sample and the standard as indicated above. AML 193.1.3 cells proliferate in response to hIL-3, hGM-CSF and hG-CSF. Therefore the

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following additional assays were performed for some samples to demonstrate that the G-CSF receptor agonist portion of the multi-functional hematopoietic receptor agonist proteins was active. The proliferation assay was performed with the multifunctional hematopoietic receptor agonist plus and minus neutralizing monoclonal antibodies to the hIL-3 receptor agonist portion. In addition, a fusion molecule with the factor Xa cleavage site was cleaved then purified and the halves of the molecule were assayed for proliferative These experiments showed that both components of the multi-functional hematopoietic receptor agonist proteins were active.

TF1 c-mpl ligand dependent proliferation assay

15 [0122] The c-mpl ligand proliferative activity can be assayed using a subclone of the pluripotential human cell line TF1 (Kitamura et al., J. Cell Physiol 140:323-334. [1989]). TF1 cells are maintained in h-IL3 (100 U/mL). To establish a subclone responsive to c-mpl ligand, cells are maintained in passage media containing 10% supernatant from BHK cells transfected with the gene expressing the 1-153 form of c-mpl ligand (pMON26448). Most of the cells die, but a subset of cells survive. After dilution cloning, a c-mpl ligand responsive clone is selected, and these cells are split into

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to assay set-up. Passage media for these cells is the following: RPMI 1640 (Gibco), 10% FBS (Harlan, Lot #91206), 10% c-mpl ligand supernatant from transfected BHK cells, 1 mM sodium pyruvate (Gibco), 2 mM glutamine (Gibco), and 100 ug/mL penicillin-streptomycin (Gibco). The next day, cells are harvested and washed twice in RPMI or IMDM media with a final wash in the ATL, or assay media. ATL medium consists of the following: IMDM (Gibco), 500 ug/mL of bovine serum albumin, 100 ug/mL of human transferrin, 50 ug/mL soybean lipids, 4 x 10-8M beta-mercaptoethanol and 2 mL of A9909 (Sigma, antibiotic solution) per 1000 mL of ATL. Cells are diluted in assay media to a final density of 0.25×10^6 cells/mL in a 96-well low evaporation plate (Costar) to a final volume of 50 ul. Transient supernatants (conditioned media) from transfected clones are added at a volume of 50 ul as duplicate samples at a final concentration of 50% and diluted three-fold to a final dilution of 1.8%. Triplicate samples of a dose curve of IL-3 starting at 1 ng/mL and diluted using variant pMON13288 three-fold dilutions to 0.0014ng/mL is included as a positive control. Plates are incubated at 5% CO2 and 37° C. At day six of culture, the plate is pulsed with 0.5 Ci of 3H/well (NEN) in a volume of 20 ul/well and allowed to incubate at 5% CO2 and 37° C for four hours. The plate is harvested and counted on a Betaplate counter.

Other in vitro cell based proliferation assays

[0123] Other in vitro cell based assays, known to those skilled in the art, may also be useful to determine the activity of the multi-functional hematopoietic receptor agonists depending on the factors that comprise the molecule in a similar manner as described in the AML 193.1.3 cell proliferation assay. The following are examples of other useful assays.

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TF1 proliferation assay: TF1 is a pluripotential human cell line (Kitamura et al., J. Cell Physiol 140:323-334. [1989]) that responds to hIL-3.

32D proliferation assay: 32D is a murine IL-3 dependent
15 cell line which does not respond to human IL-3 but does
respond to human G-CSF which is not species restricted.

Baf/3 proliferation assay: Baf/3 is a murine IL-3 dependent cell line which does not respond to human IL-3 or human c-mpl ligand but does respond to human G-CSF which is not species restricted.

T1165 proliferation assay: T1165 cells are a IL-6 dependent murine cell line (Nordan et al., 1986) which respond to IL-6 and IL-11.

Human Plasma Clot meg-CSF Assay: Used to assay 25 megakaryocyte colony formation activity (Mazur et al., 1981).

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Transfected cell lines

[0124] Cell lines such as the murine Baf/3 cell line can be transfected with a colony stimulating factor receptor, such as the human G-CSF receptor or human c-mpl receptor, which the cell line does not have. These transfected cell lines can be used to determine the activity of the ligand for which the receptor has been transfected into the cell line.

[0125] One such transfected Baf/3 cell line was made by cloning the cDNA encoding c-mpl from a library made from a c-mpl responsive cell line and cloned into the multiple cloning site of the plasmid pcDNA3 (Invitrogen, San Diego Ca.). Baf/3 cells were transfected with the plasmid via electroporation. The cells were grown under G418 selection in the presence of mouse IL-3 in Wehi conditioned media. Clones were established through limited dilution.

[0126] In a similar manner the human G-CSF receptor can be transfected into the Baf/3 cell line and used to determine the bioactivity of the multi-functional hematopoietic receptor agoinsts.

Analysis of c-mpl ligand proliferative activity Methods

- 1. Bone marrow proliferation assay
- 25 a. CD34+ Cell Purification:

Bone marrow aspirates (15-20 mL) were obtained from

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normal allogeneic marrow donors after informed consent. Cells were diluted 1:3 in phosphate buffered saline (PBS, Gibco-BRL), 30 mL were layered over 15 mL Histopaque-1077 (Sigma) and centrifuged for 30 minutes at 300 RCF. The mononuclear interface layer was collected and washed in PBS. CD34+ cells were enriched from the mononuclear cell preparation using an affinity column per manufacturers instructions (CellPro, Inc, Bothell WA). After enrichment, the purity of CD34+ cells was 70% on average as determined by using flow cytometric analysis using anti-CD34 monoclonal antibody conjugated to fluorescein and anti-CD38 conjugated to phycoerythrin (Becton Dickinson, San Jose CA).

Cells were resuspended at 40,000 cells/mL in X-Vivo 10 media (Bio-Whittaker, Walkersville, MD) and 1 mL was plated in 12-well tissue culture plates (Costar). The growth factor rhIL-3 was added at 100 ng/mL (pMON5873) was added to some hIL3 variants were used at 10 ng/mL to 100 ng/mL. Conditioned media from BHK cells transfected with plasmid encoding or multi-functional c-mpl ligand hematopoietic receptor agonists were tested by addition of 100 µl supernatant added to 1 mL cultures (approximately a 10% Cells were incubated at 37°C for 8-14 days at 5% dilution). CO2 in a 37°C humidified incubator.

b. Cell Harvest and Analysis:

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At the end of the culture period a total cell count was obtained for each condition. For fluorescence analysis and ploidy determination cells were washed in megakaryocyte buffer (MK buffer, 13.6 mM sodium citrate, 1 mM theophylline, 2.2 µm PGE1, 11 mM glucose, 3% w/v BSA, in PBS, pH 7.4,) (Tomer et al., Blood 70: 1735-1742, 1987) resuspended in 500 µl of MK buffer containing anti-CD41a FITC antibody (1:200, AMAC, Westbrook, ME) and washed in MK buffer. For DNA analysis cells were permeablized in MK buffer containing 0.5% Tween 20 (Fisher, Fair Lawn NJ) for 20 min. on ice followed by fixation in 0.5% Tween-20 and 1% paraformaldehyde (Fisher Chemical) for minutes followed by incubation in propidium (Calbiochem , La Jolla Ca) (50 μ g/mL) with RNA-ase (400 U/mL) in 55% v/v MK buffer (200mOsm) for 1-2 hours on ice. were analyzed on a FACScan or Vantage flow cytometer (Becton Dickinson, San Jose, CA). Green fluorescence (CD41a-FITC) was collected along with linear and log signals for fluorescence (PI) to determine DNA ploidy. All cells were collected to determine the percent of cells that were CD41+. Data analysis was performed using software by LYSIS (Becton Dickinson, San Jose, CA). Percent of cells expressing the CD41 antigen obtained was from flow cytometry analysis (Percent). Absolute (Abs) number of CD41+ cells/mL was calculated by: (Abs) = (Cell Count) * (Percent) / 100.

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2. Megakaryocyte fibrin clot assay.

CD34+ enriched population were isolated as described Cells were suspended at 25,000 cells/mL with or without cytokine(s) in a media consisting of a base Iscoves IMDM media supplemented with 0.3% BSA, 0.4mg/mL apotransferrin, 6.67µM FeCl₂, 25µg/mL CaCl2, 25µg/mL L-500µg/mL asparagine, e-amino-n-caproic acid and penicillin/streptomycin. Prior to plating into 35mm plates, thrombin was added (0.25 Units/mL) to initiate clot formation. Cells were incubated at 37°C for 13 days at 5% CO2 in a 37°C humidified incubator.

At the end of the culture period plates were fixed with methanol:acetone (1:3), air dried and stored at -200C until staining. A peroxidase immunocytochemistry staining procedure was used (Zymed, Histostain-SP. San Francisco, CA) using a cocktail of primary monoclonal antibodies consisting of anti-CD41a, CD42 and CD61. Colonies were counted after staining and classified as negative, CFU-MK (small colonies, 1-2 foci and less that approx. 25 cells), BFU-MK (large, multi-foci colonies with > 25 cells) or mixed colonies (mixture of both positive and negative cells.

Methylcellulose Assay

[0127] This assay reflects the ability of colony stimulating factors to stimulate normal bone marrow cells to produce

different types of hematopoietic colonies in vitro (Bradley et al., Aust. Exp Biol. Sci. 44:287-300, 1966), Pluznik et al., J. Cell Comp. Physio 66:319-324, 1965).

Methods

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Approximately 30 mL of fresh, normal, healthy bone marrow aspirate are obtained from individuals following informed Under sterile conditions samples are diluted 1:5 with a 1X PBS (#14040.059 Life Technologies, Gaithersburg, MD.) solution in a 50 mL conical tube (#25339-50 Corning, 10 Corning MD). Ficoll (Histopaque 1077 Sigma H-8889) is layered under the diluted sample and centrifuged, 300 x g for 30 min. The mononuclear cell band is removed and washed two times in 1X PBS and once with 1% BSA PBS (CellPro Co., Bothel, WA). 15 Mononuclear cells are counted and CD34+ cells are selected using the Ceprate LC (CD34) Kit (CellPro Co., Bothel, WA) This fractionation is performed since all stem and progenitor cells within the bone marrow display CD34 surface antigen.

- Cultures are set up in triplicate with a final volume of 1.0 mL in a 35 X 10 mm petri dish (Nunc#174926). Culture medium is purchased from Terry Fox Labs. (HCC-4230 medium (Terry Fox Labs, Vancouver, B.C., Canada) and erythropoietin (Amgen, Thousand Oaks, CA.) is added to the culture media.
- 25 3,000-10,000 CD34+ cells are added per dish. Recombinant IL-3,

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purified from mammalian cells or *E. coli*, and multi-functional hematopoietic receptor agonist proteins, in conditioned media from transfected mammalian cells or purified from conditioned media from transfected mammalian cells or *E. coli*, are added to give final concentrations ranging from .001 nM to 10 nM. Recombinant hIL-3, GM-CSF, c-mpl ligand and multi-functional hematopoietic receptor agonist are supplied in house. G-CSF (Neupogen) is from Amgen (Thousand Oaks Calf.). Cultures are resuspended using a 3cc syringe and 1.0 mL is dispensed per dish. Control (baseline response) cultures received no colony stimulating factors. Positive control cultures received conditioned media (PHA stimulated human cells: Terry Fox Lab. H2400). Cultures are incubated at 37°C, 5% CO₂ in humidified air.

Hematopoietic colonies which are defined as greater than 50 cells are counted on the day of peak response (days 10-11) using a Nikon inverted phase microscope with a 40x objective combination. Groups of cells containing fewer than 50 cells are referred to as clusters. Alternatively colonies can be identified by spreading the colonies on a slide and stained or they can be picked, resuspended and spun onto cytospin slides for staining.

Human Cord Blood Hemopoietic Growth Factor Assays

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Methods

[0128] Bone marrow cells are traditionally used for in vitro assays of hematopoietic colony stimulating factor activity. However, human bone marrow is not always available, is considerable variability between and there Umbilical cord blood is comparable to bone marrow as a source of hematopoietic stem cells and progenitors (Broxmeyer et al., PNAS USA 89:4109-113, 1992; Mayani et al., Blood 81:3252-3258, 1993). In contrast to bone marrow, cord blood is more readily available on a regular basis. There is also a potential to reduce assay variability by pooling cells obtained fresh from several donors, or to create a bank of cryopreserved cells for this purpose. By modifying the culture conditions, and/or analyzing for lineage specific markers, it is be possible to assay specifically for granulocyte / macrophage colonies (CFU-GM), for megakaryocyte CSF activity, or for high proliferative potential colony forming cell (HPP-CFC) activity.

Mononuclear cells (MNC) are isolated from cord blood 20 within 24 hr. of collection, using a standard density gradient (1.077 g/mL Histopaque). Cord blood MNC have been further enriched for stem cells and progenitors by several procedures, including immunomagnetic selection for CD14-, CD34+ cells; panning for SBA-, CD34+ fraction using coated flasks from 25 Applied Immune Science (Santa Clara, CA); and CD34+ selection

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using a CellPro (Bothell, WA) avidin column. Either freshly isolated or cryopreserved CD34+ cell enriched fractions are used for the assay. Duplicate cultures for each serial dilution of sample (concentration range from 1 pM to 1204 pM) are prepared with 1x104 cells in 1ml of 0.9% methycellulose containing medium without additional growth factors (Methocult H4230 from Stem Cell Technologies, Vancouver, BC.). In some experiments, Methocult H4330 containing erythropoietin (EPO) was used instead of Methocult H4230, or Stem Cell Factor (SCF), 50 ng/mL (Biosource International, Camarillo, CA) was added. After culturing for 7-9 days, colonies containing >30 cells are counted. In order to rule out subjective bias in scoring, assays are scored blind.

Additional details about recombinant DNA methods which may be used to create the variants, express them in bacteria, mammalian cells or insect cells, purification and refold of desired proteins and assays for determining bioactivity of the proteins may be found in co-filed Applications WO 95/00646, WO 94/12639, WO 94/12638, WO 95/20976, WO 95/21197, WO 95/20977, WO 95/21254 08/383,035 which are hereby incorporated by reference in their entirety.

Further details known to those skilled in the art may be found in T. Maniatis, et al., Molecular Cloning, A Laboratory

Manual, Cold Spring Harbor Laboratory, 1982) and references cited therein, incorporated herein by reference; and in J. Sambrook, et al., Molecular Cloning, A Laboratory Manual, 2nd edition, Cold Spring Harbor Laboratory, 1989) and references cited therein, are incorporated herein by reference.

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TABLE 1 OLIGONUCLEOTIDES

5	c-mplNcoI ACGTCCATGO (SEQ ID NO N=A,C,G or T	GCNTCNCCNGCNCCTGCTTGTGCACTCCGAGTC D: 13)
10	Ecompl	ATGCACGAATTCCCTGACGCAGAGGGTGGA (SEQ ID NO:14)
	c-mplHindIII	TGACAAGCTTACCTGACGCAGAGGGTGGACCCT (SEQ ID NO:15)
15	4L-5'	AATTCGGCAA (SEQ ID NO:16)
	4L-3'	CATGTTGCCG (SEQ ID NO:17)
20	5L-5'	AATTCGGCGGCAA (SEQ ID NO:18)
	5L-3'	CATGTTGCCGCCG (SEQ ID NO:19)
	8L-5'	AATTCGGCGGCAACGGCGGCAA (SEQ ID NO:20)
25	8L-3'	CATGTTGCCGCCGTTGCCGCCG (SEQ ID NO:21)
	31-5'	CGATCCATGGAGGTTCACCCTTTGCCT (SEQ ID NO:22)
30	31-3'	GATCAAGCTTATGGGCACTGGCTCAGTCT (SEQ ID NO:23)
	35-5'	CGATACATGTTGCCTACACCTGTCCTG (SEQ ID NO:24)
	35-3'	GATCAAGCTTAAGGGTGAACCTCTGGGCA (SEQ ID NO:25)
35	39-5'	CGATCCATGGTCCTGCTGCTGTG (SEQ ID NO:26)
	39-3'	GATCAAGCTTAAGGTGTAGGCAAAGGGTG (SEQ ID NO:27)
40	43-5'	CGATCCATGGCTGTGGACTTTAGCTTGGGA (SEQ ID NO:28)
	43-3'	GATCAAGCTTAAGGCAGCAGGACAGGTGT (SEQ ID NO:29)
	45-5'	CGATCCATGGACTTTAGCTTGGGAGAA (SEQ ID NO:30)
45	45-3'	GATCAAGCTTACACAGCAGCAGCAGGAC (SEQ ID NO:31)
	49-5'	CGATCCATGGGAGAATGGAAAACCCAG (SEQ ID NO:32)

	49-3'	GATCAAGCTTACAAGCTAAAGTCCACAGC (SEQ ID NO:33)
5	82-5'	CGATCCATGGGACCCACTTGCCTCTCA (SEQ ID NO:34)
3	82-3'	GATCAAGCTTACAGTTGTCCCCGTGCTGC (SEQ ID NO:35)
	109-5'	CAGTCCATGGGAACCCAGCTTCCTCCA (SEQ ID NO:36)
10	109-3'	GATCAAGCTTAAAGGAGGCTCTGCAGGGC (SEQ ID NO:37)
	116-5'	CGATCCATGGGCAGGACCACAGCTCAC (SEQ ID NO:38)
15	116-3'	GATCAAGCTTACTGTGGAGGAAGCTGGGTT (SEQ ID NO:39)
13	120-5'	CGATCCATGGCTCACAAGGATCCCAATGCC (SEQ ID NO:40)
	120-3'	GATCAAGCTTATGTGGTCCTGCCCTGTGG (SEQ ID NO:41)
20	123-5'	CGATCCATGGATCCCAATGCCATCTTCCTG (SEQ ID NO:42)
	123-3'	GATCAAGCTTACTTGTGAGCTGTGGTCCT (SEQ ID NO:43)
25	126-5′	CGATCCATGGCCATCTTCCTGAGCTTCCAA (SEQ ID NO:44)
	126-3'	GATCAAGCTTAATTGGGATCCTTGTGAGCTGT (SEQ ID NO:45)
30	SYNNOXA1.REQ	AATTCCGTCG TAAACTGACC TTCTATCTGA AAACCTTGGA GAACGCGCAG GCTCAACAGT ACGTAGAGGG CGGTGGAGGC TCC (SEQ ID NO:46)
35	SYNNOXA2.REQ	CCGGGGAGCC TCCACCGCCC TCTACGTACT GTTGAGCCTG CGCGTTCTCC AAGGTTTTCA GATAGAAGGT CAGTTTACGA CGG (SEQ ID NO:47)
40	Llsyn.for	GTTACCCTTG AGCAAGCGCA GGAACAACAG GGTGGTGGCT CTAACTGCTC TATAATGAT (SEQ ID NO:48)
40	L1syn.rev	CGATCATTAT AGAGCAGTTA GAGCCACCAC CCTGTTGTTC CTGCGCTTGC TCAAGG (SEQ ID NO:49)
45	L3syn.for	GTTACCCTTG AGCAAGCGCA GGAACAACAG GGTGGTGGCT CTGGCGGTGG CAGCGGCGGC GGTTCTAACT GCTCTATAAT GAT (SEQ ID NO:50)

	L3syn.rev	CGATCATTAT AGAGCAGTTA GAACCGCCGC CGCTGCCACC GCCAGAGCCA CCACCCTGTT GTTCCTGCGC TTGCTCAAGG (SEQ ID NO:51)
5	35start.seq	GATCGACCAT GGCTCTGGAC CCGAACAACC TC (SEQ ID NO:52)
	34rev.seq	CTCGATTACG TACAAAGGTG CAGGTGGT (SEQ ID NO:53)
10	70start.seq	GATCGACCAT GGCTAATGCA TCAGGTATTG AG (SEQ ID NO:54)
	69rev.seq	CTCGATTACG TATTCTAAGT TCTTGACA (SEQ ID NO:55)
15	91start.seq	GATCGACCAT GGCTGCACCC TCTCGACATC CA (SEQ ID NO:56)
	90rev.seq	CTCGATTACG TAGGCCGTGG CAGAGGGC (SEQ ID NO:57)
20	101start.seq	GATCGACCAT GGCTGCAGGT GACTGGCAAG AA (SEQ ID NO:58)
	100rev.seq	CTCGATTACG TACTTGATGA TGATTGGA (SEQ ID NO:59)
25	L-11start.seq	GCTCTGAGAG CCGCCAGAGGG CTGCGCAAGG TGGCGTAGAA CGCG (SEQ ID NO:60)
30	L-11stop.seq	CAGCCCTCTG GCGGCTCTGG CGGCTCTCAG AGCTTCCTGC TCAAGTCTTT AGAG (SEQ ID NO:61)
50	P-blstart.seq	GGGCTGCGCA AGGTGGCG (SEQ ID NO:62)
	P-blstop.seq	ACACCATTGG GCCCTGCCAG C (SEQ ID NO:63)
35	39start.seq	GATCGACCAT GGCTTACAAG CTGTGCCACC CC (SEQ ID NO:64)
40	38stop.Seq	CGATCGAAGC TTATTAGGTG GCACACAGCT TCTCCT (SEQ ID NO:65)
40	97start.seq	GATCGACCAT GGCTCCCGAG TTGGGTCCCA CC (SEQ ID NO:66)
45	96stop.Seq	CGATCGAAGC TTATTAGGAT ATCCCTTCCA GGGCCT (SEQ ID NO:67)
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		(SEQ ID NO:68)
_	125stop.Seq	CGATCGAAGC TTATTATCCC AGTTCTTCCA TCTGCT (SEQ ID NO:69)
5	133start.seq	GATCGACCAT GGCTACCCAG GGTGCCATGC CG (SEQ ID NO:70)
10	132stop.seq	CGATCGAAGC TTATTAGGGC TGCAGGGCAG GGGCCA (SEQ ID NO:71)
	142start.seq	GATCGACCAT GGCTTCTGCT TTCCAGCGCC GG (SEQ ID NO:72)
15	141stop.Seq	CGATCGAAGC TTATTAGGCG AAGGCCGGCA TGGCAC (SEQ ID NO:73)
	GLYXA1	GTAGAGGCCG GTGGAGGCTC C (SEQ ID NO:74)
20	GLYXA2	CCGGGGAGCC TCCACCGCCC TCTAC (SEQ ID NO:75)
	1GGGSfor	TTCTACGCCA CCTTGCGCAG CCCGGCGGCG GCTCTGACAT GTCTACACCA TTG (SEQ ID NO:76)
25	1GGGSrev	CAATGGTGTA GACATGTCAG AGCCGCCGCC GGGCTGCGCA AGGTGGCGTA GAA (SEQ ID NO:77)
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Synnoxal.req AATTCCGTCG TAAACTGACC TTCTATCTGA AAACCTTGGA
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TCC (SEQ ID NO:240)

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CGG (SEQ ID NO:241)

35 <u>TABLE 2</u> GENE SEQUENCES

pMON30304

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pMON26458

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pMON28502

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Syntan1

TCCACCCTCTGCGTCAGG (SEQ ID NO:83)

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CAGTAC (SEQ ID NO:84)

Syntan3

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20	251	CCAATCATCA	TCAAGGCAGG	TGACTGGCAA	GAATTCCGGG	AAAAACTGAC
	301	GTTCTATCTG	GTTACCCTTG	AGCAAGCGCA	GGAACAACAG	GGTGGTGGCT
	351	CTGGCGGTGG	CAGCGGCGGC	GGTTCTAACT	GCTCTATAAT	GATCGATGAA
	401	ATTATACATC	ACTTAAAGAG	ACCACCTGCA	CCTTTGCTGG	ACCCGAACAA
	451	CCTCAATGAC	GAAGACGTCT	CTATCCTGAT	GGACCGAAAC	CTTCGACTTC
25	501	CAAACCTGGA	GAGCTTCGTA	AGGGCTGTCA	AGAACTTAGA	AAATGCATCA
	551	GGTATTGAGG	CAATTCTTCG	TAATCTCCAA	CCATGTCTGC	CCTCTGCCAC
	601	GGCCGCACCC	TCTCGACATC	CAATCATCAT	CAAGGCAGGT	GACTGGCAAG
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	701	GAACAACAGT	AC (SEQ ID	NO:85)		
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	351	GTACGTAGAG	GGCGGTGGAG	GCTCCCGGG	TGAACCGTCT	GGTCCAATCT
	401	CTACTATCAA	CCCGTCTCCT	CCGTCTAAAG	AATCTCATAA	ATCTCCAAAC
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45	551	CGTACCGCGT	TCTACGCCAC	CTTGCGCAGC	CCTCTGGCGG	CTCTGGCGGC
	601	TCTCAGAGCT	TCCTGCTCAA	GTCTTTAGAG	CAAGTGAGAA	AGATCCAGGG
	651	CGATGGCGCA	GCGCTCCAGG	AGAAGCTGTG	TGCCACCTAC	AAGCTGTGCC

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701 ACCCCGAGGA GCTGGTGCTG CTCGGACACT CTCTGGGCAT CCCCTGGGCT
751 CCCCTGAGCT CCTGCCCCAG CCAGGCCCTG CAGCTGGCAG GCTGCTTGAG
801 CCAACTCCAT AGCGGCCTTT TCCTCTACCA GGGGCTCCTG CAGGCCCTGG
851 AAGGGATATC CCCCGAGTTG GGTCCCACCT TGGACACACT GCAGCTGGAC
5 901 GTCGCCGACT TTGCCACCAC CATCTGGCAG CAGATGGAAG AACTGGGAAT
951 GGCCCCTGCC CTGCAGCCCT AATAA (SEQ ID NO:86)
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pMON31105

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40	251	ACCTGGAGAG	CTTCGTAAGG	GCTGTCAAGA	ACTTAGAAAA	TGCATCAGGT
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10 pMON31107

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	251	ACTTAGAAAA	TGCATCAGGT	ATTGAGGCAA	TTCTTCGTAA	TCTCCAACCA
	301	TGTCTGCCCT	CTGCCACGGC	CGCACCCTCT	CGACATCCAA	TCATCATCAA
	351	GTACGTAGAG	GGCGGTGGAG	GCTCCCCGGG	TGAACCGTCT	GGTCCAATCT
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pMON31111

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pMON31113

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pMON31115

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pMON28505

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NO:118)

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pMON28506

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pMON28507

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TTCACAGCAGACTGAGCCAGAGGTTCACCCTTTGCCTACACCT (SEQ ID NO:120)

5 pMON28508

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25 pMON28509

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pMON28512

GCTAACTGCTCTATAATGATCGATGAAATTATACATCACTTAAAGAGACCACCTGCACCTTT
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 TCTGGTCCAATCTCTACTATCAACCCGTCTCCTCCGTCTAAAGAATCTCATAAATCTCCAAA
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ACCCTCTGCGTCAGGGAATTCGGCGGCAACATGGCGTCTCCCGCCTCCGCCTTGTGACCT
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CAGAGGTTCACCCTTTGCCTACACCTGTCCTGCTGCTGTGGACTTTAGCTTGGGAGAA
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GGAGGGAGTGATGGCAGCACGGGGACAACTGGGACCCACTTGCCTCCTCGTGGGC
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(SEQ ID
NO:125)

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pMON28513

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pMON28514

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5 pMON28515

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25 pMON28516

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pMON28520

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pMON28521

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GCAATTCTTCGTAATCTCCAACCATGTCTGCCCTCTGCCACGGCCGCACCCTCTCGACATCC
45 AATCATCAAGGCAGGTGACTGGCAAGAATTCCGGGAAAAACTGACGTTCTATCTGGTTA
CCCTTGAGCAAGCGCAGGAACAACAGTACGTAGAGGCGGTGGAGGCTCCCCGGGTGAACCG
TCTGGTCCAATCTCTACTATCAACCCGTCTCCCTCCGTCTAAAGAATCTCATAAATCTCCAAA

CATGGTCCTGCTGCTGTGGACTTTAGCTTGGGAGAATGGAAAACCCAGATGGAGGAGA CCAAGGCACAGGACATTCTGGGAGCAGTGACCCTTCTGCTGGAGGAGTGATGGCAGCACGG GGACAACTGGGACCACTTCCTCTCTCTCTCTCTGGACAGCTTCTTCTGGACAGGTCCGTCT CCTCCTTGGGACCCACTTCCTCACAGGGCAGGACCACAG CTCACAAGGATCCCAATGCCATCTTCCTGAGCTTCCAACACCTGCTCCGAGGAAAGGTGCGT TTCCTGATGCTTGTAGGAGGGTCCACCCTCTGCGTCAGGAATTCGGCAACATGCCGTCTCC CGCTCCGCCTGCTTGTGACCTCCGAGTCCTCC ACAGCAGACTGACCTCCCATGTCCTTC ACAGCAGACTGAGCCAGTGCCCAGGTTCACCCTTTGCCTACACCT (SEQ ID NO: 132)

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pMON28522

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5 pMON28524

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25 pMON28525

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GCTAACTGCTCTATAATGATCGATGAAATTATACATCACTTAAAGAGACCACCTGCACCTTT GCTGGACCCGAACACCTCAATGACGAAGACGTCTCTATCCTGATGGACCGAAACCTTCGAC TTCCAAACCTGGAGAGCTTCGTAAGGGCTGTCAAGAACTTAGAAAATGCATCAGGTATTGAG GCAATTCTTCGTAATCTCCAACCATGTCTGCCCTCTGCCACGGCCGCACCCTCTCGACATCC 5 AATCATCATCAAGGCAGGTGACTGGCAAGAATTCCGGGAAAAACTGACGTTCTATCTGGTTA CCCTTGAGCAAGCGCAGGAACAACAGTACGTAGAGGGCGGTGGAGGCTCCCCGGGTGAACCG TCTGGTCCAATCTCTACTATCAACCCGTCTCCCTCCGTCTAAAGAATCTCATAAATCTCCAAA CATGGGAACCCAGCTTCCTCCACAGGGCAGGACCACAGCTCACAAGGATCCCAATGCCATCT TCCTGAGCTTCCAACACCTGCTCCGAGGAAAGGTGCGTTTCCTGATGCTTGTAGGAGGGTCC 10 ACCCTCTGCGTCAGGGAATTCGGCAACATGGCGTCTCCCGCCTGCTTGTGACCTCCG AGTCCTCAGTAAACTGCTTCGTGACTCCCATGTCCTTCACAGCAGACTGAGCCAGTGCCCAG AGGTTCACCCTTTGCCTACACCTGTCCTGCTGCTGTGGACTTTAGCTTGGGAGAATGG AAAACCCAGATGGAGGAGACCAAGGCACATTCTGGGAGCAGTGACCCTTCTGCTGGA GGGAGTGATGCCACGGGGACAACTGGGACCCACTTGCCTCTCATCCCTCCTGGGGCAGC 15 TTTCTGGACAGGTCCGTCTCCTTGGGGCCCTGCAGAGCCTCCTT (SEQ ID NO:137)

pMON28527

20 GCTAACTGCTCTATAATGATCGATGAAATTATACATCACTTAAAGAGACCACCTGCACCTTT GCTGGACCCGAACACCTCAATGACGAAGACGTCTCTATCCTGATGGACCGAAACCTTCGAC TTCCAAACCTGGAGAGCTTCGTAAGGGCTGTCAAGAACTTAGAAAATGCATCAGGTATTGAG GCAATTCTTCGTAATCTCCAACCATGTCTGCCCTCTGCCACGGCCGCACCCTCTCGACATCC 25 AATCATCAAGGCAGGTGACTGGCAAGAATTCCGGGAAAAACTGACGTTCTATCTGGTTA CCCTTGAGCAAGCGCAGGAACAACAGTACGTAGAGGGCGGTGGAGGCTCCCCGGGTGAACCG TCTGGTCCAATCTCTACTATCAACCCGTCTCCTCCGTCTAAAGAATCTCATAAATCTCCAAA CATGGGCAGGACCACAGCTCACAAGGATCCCAATGCCATCTTCCTGAGCTTCCAACACCTGC TCCGAGGAAAGGTGCGTTTCCTGATGCTTGTAGGAGGGTCCACCCTCTGCGTCAGGGAATTC 30 GGCAACATGGCGTCTCCGCTTCGCTTGTGACCTCCGAGTCCTCAGTAAACTGCTTCG TGACTCCCATGTCCTTCACAGCAGACTGAGCCAGTGCCCAGAGGTTCACCCTTTGCCTACAC CTGTCCTGCTGCTGTGGACTTTAGCTTGGGAGAATGGAAAACCCAGATGGAGGAGACC ACAACTGGGACCCACTTGCCTCTCATCCCTCCTGGGGCAGCTTTCTGGACAGGTCCGTCTCC 35 TCCTTGGGGCCCTGCAGAGCCTCCTTGGAACCCAGCTTCCTCCACAG NO:138)

pMON28528

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GCTAACTGCTCTATAATGATCGATGAAATTATACATCACTTAAAGAGACCACCTGCACCTTT
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GCAATTCTTCGTAATCTCCAACCATGTCTGCCCTCTGCCACGGCCGCACCCTCTCGACATCC
45
AATCATCATCAAGGCAGGTGACTGGCAAGAATTCCGGGAAAAACTGACGTTCTATCTGGTTA
CCCTTGAGCAAGCCAGGAACAACAGTACGTAGAGGCGGTGGAGGCTCCCCGGGTGAACCG
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pMON28529

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pMON28530

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5 pMON28533

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25 pMON28534

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GCTAACTGCTCTATAATGATCGATGAAATTATACATCACTTAAAGAGACCACCTGCACCTTT GCTGGACCCGAACACCTCAATGACGAAGACGTCTCTATCCTGATGGACCGAAACCTTCGAC TTCCAAACCTGGAGAGCTTCGTAAGGGCTGTCAAGAACTTAGAAAATGCATCAGGTATTGAG GCAATTCTTCGTAATCTCCAACCATGTCTGCCCTCTGCCACGGCCGCACCCTCTCGACATCC 5 AATCATCAAGGCAGGTGACTGGCAAGAATTCCGGGAAAAACTGACGTTCTATCTGGTTA CCCTTGAGCAAGCGCAGGAACAACAGTACGTAGAGGGCGGTGGAGGCTCCCCGGGTGAACCG TCTGGTCCAATCTCTACTATCAACCCGTCTCCTCCGTCTAAAGAATCTCATAAATCTCCAAA CATGGTCCTGCTGCTGTGGACTTTAGCTTGGGAGAATGGAAAACCCAGATGGAGGAGA 10 GGACAACTGGGACCCACTTGCCTCTCATCCCTCCTGGGGCAGCTTTCTGGACAGGTCCGTCT CCTCCTTGGGGCCCTGCAGAGCCTCCTTGGAACCCAGCTTCCTCCACAGGGCAGGACCACAG CTCACAAGGATCCCAATGCCATCTTCCTGAGCTTCCAACACCTGCTCCGAGGAAAGGTGCGT TTCCTGATGCTTGTAGGAGGGTCCACCCTCTGCGTCAGGGAATTCGGCGGCAACGGCGGCAA CATGGCGTCCCAGCGCCGCCTGCTTGTGACCTCCGAGTCCTCAGTAAACTGCTTCGTGACT 15 CCCATGTCCTTCACAGCAGACTGAGCCAGTGCCCAGAGGTTCACCCTTTGCCTACACCT (SEO ID NO:144)

pMON28536

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GCTAACTGCTCTATAATGATCGATGAAATTATACATCACTTAAAGAGACCACCTGCACCTTT
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TTCCAAACCTGGAGAGCTTCGTAAGGGCTGTCAAGAACTTAGAAAATGCATCAGGTATTGAG
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25 AATCATCAAGGCAGGTGACTGGCAAGAATTCCGGGAAAAACTGACGTTCTATCTGGTTA
CCCTTGAGCAAGCGCAGGAACAACAGTACGTAGAGGGCGGTGGAGCTCCCCGGGTGAACCG
TCTGGTCCAATCTCTACTATCAACCCGTCTCCCTCCTCAAAGAATCTCCAAA

CATGGCTGTGGACTTTAGCTTGGGAGAATGGAAAACCCAGATGGAGGAGCACAGG ACATTCTGGGAGCAGTGACCCTTCTGCTGGAGGGAGTGATGGCAGCACGGGGACAACTGGGA CCCACTTGCCTCTCATCCCTCCTGGGGCAGCTTTCTGGACAGGTCCGTCTCCTCCTTGGGGC CCTGCAGAGCCTCCTTGGAACCCAGCTTCCTCCACAGGGCAGGACCACAGCTCACAAGGATC CCAATGCCATCTTCCTGAGCTTCCAACACCTGCTCCGAGGAAAGGTGCGTTTCCTGATGCTT GTAGGAGGGTCCACCCTCTGCGTCAGGAATTCGGCGCGAACAGGCGCAACATGCCTCCC AGCGCCGCCTGCTTGTGACCTCCGAGTCCTCAGTAAACTGCTTCGTGACTCCCATGTCCTTC

35 ACAGCAGACTGAGCCAGAGGTTCACCCTTTGCCTACACCTGTCCTGCCT (SEQ ID NO:145)

pMON28537

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45
AATCATCATCAAGGCAGGTGACTGGCAAGAATTCCGGGAAAAACTGACGTTCTATCTGGTTA
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TGGGAGCAGTGACCCTTCTGCTGGAGGGAGTGATGGCAGCACGGGGACAACTGGGACCCACT
TGCCTCTCATCCCTCCTGGGGCAGCTTTCTGGACAGGTCCGTCTCCTCCTTGGGGCCCTGCA
GAGCCTCCTTGGAACCCAGCTTCCTCCACAGGGCAGGACCACAGCTCACAAGGATCCCAATG
CCATCTTCCTGAGCTTCCAACACCTGCTCCGAGGAAAGGTGCGTTTCCTGATGCTTGTAGGA
GGGTCCACCCTCTGCGTCAGGGAATTCGGCGGCAACATGGCGTCCCCAGCGCC
GCCTGCTTGTGACCTCCGAGTCCTCAGTAAACTGCTTCGTGACTCCCATGTCCTTCACAGCA
GACTGAGCCAGTGCCCAGAGGTTCACCCTTTGCCTACACCTGTCCTGCTGCTGC
(SEQ ID NO:146)

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pMON28538

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pMON28539

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GCCTGCTGTGGACTTTAGCTTGGGAGAATGGAAAACCCAGATGGAGGAGACCAAGGCACAGG ACATTCTGGGAGCAGTGACCCTTCTGCTGGAGGGAGTGATGGCAGCACGGGACAACTG (SEQ ID NO:148)

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pMON28540

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pMON28541

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pMON28543

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pMON28544

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GCAATTCTTCGTAATCTCCAACCATGTCTGCCCTCTGCCACGGCCGCACCCTCTCGACATCC
45 AATCATCAAGGCAGGTGACTGGCAAGAATTCCGGGAAAAACTGACGTTCTATCTGGTTA
CCCTTGAGCAAGCCAGGAACAACAGTACGTAGAGGGCGGTGGAGGCTCCCCGGGTGAACCG
TCTGGTCCAATCTCTACTATCAACCCGTCTCCTCCGTCTAAAGAATCTCATAAATCTCCAAA

CATGGCCATCTTCCTGAGCTTCCAACACCTGCTCCGAGGAAAGGTGCGTTTCCTGATGCTTG
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GCGCCGCCTGCTTGTGACCTCCGAGTCCTCAGTAAACTGCTTCGTGACTCCCATGTCCTTCA
CAGCAGACTGAGCCAGTGCCCAGAGGTTCACCCTTTGCCTACACCTGTCCTGCTGCTGCTG
TGGACTTTAGCTTGGGAGAATGGAAAACCCAGATGGAGGAGACCAAGGCACAGGACATTCTG
GGAGCAGTGACCCTTCTGCTGGAGGAGTGATGGCAGCACGGGGACAACTGGGACCCACTTG
CCTCTCATCCCTCCTGGGGCAGCTTTCTGGACAGGTCCGTCTCCTCCTTGGGGCCCTGCAGA
GCCTCCTTGGAACCCAGCTTCCTCCACAGGGCAGACCACAGCTCACAAGGATCCCAAT
(SEQ ID NO:153)

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pMON28545

GCTAACTGCTCTATAATGATCGATGAAATTATACATCACTTAAAGAGACCACCTGCACCTTT 15 GCTGGACCCGAACACCTCAATGACGAAGACGTCTCTATCCTGATGGACCGAAACCTTCGAC TTCCAAACCTGGAGAGCTTCGTAAGGGCTGTCAAGAACTTAGAAAATGCATCAGGTATTGAG GCAATTCTTCGTAATCTCCAACCATGTCTGCCCTCTGCCACGGCCGCACCCTCTCGACATCC AATCATCAAGGCAGGTGACTGGCAAGAATTCCGGGAAAAACTGACGTTCTATCTGGTTA CCCTTGAGCAAGCGCAGGAACAACAGTACGTAGAGGGCGGTGGAGGCTCCCCGGGTGAACCG 20 TCTGGTCCAATCTCTACTATCAACCCGTCTCCTCCGTCTAAAGAATCTCATAAATCTCCAAA CATGGATCCCAATGCCATCTTCCTGAGCTTCCAACACCTGCTCCGAGGAAAGGTGCGTTTCC TGATGCTTGTAGGAGGGTCCACCCTCTGCGTCAGGGAATTCGGCGGCAACATGGCGTCTCCC GCTCCGCCTGCTTGTGACCTCCGAGTCCTCAGTAAACTGCTTCGTGACTCCCATGTCCTTCA 25 TGGACTTTAGCTTGGGAGAATGGAAAACCCAGATGGAGGAGACCAAGGCACAGGACATTCTG GGAGCAGTGACCCTTCTGCTGGAGGGAGTGATGGCAGCACGGGGACAACTGGGACCCACTTG CCTCTCATCCCTCCTGGGGCAGCTTTCTGGACAGGTCCGTCTCCTTCGTTGGGGCCCTGCAGA GCCTCCTTGGAACCCAGGGCAGGACCACAGCTCACAAG (SEQ ID NO:154)

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         ACCACCTGCA CCTTTGCTGG ACCCGAACAA CCTCAATGAC GAAGACGTCT
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    151
         AGGGCTGTCA AGAACTTAGA AAATGCATCA GGTATTGAGG CAATTCTTCG
    201
         TAATCTCCAA CCATGTCTGC CCTCTGCCAC GGCCGCACCC TCTCGACATC
    251
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    301
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    401
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751 GCCTCTGCTT TCCAGCGCCG GGCAGGAGGG GTCCTGGTTG CTAGCCATCT
801 GCAGAGCTTC CTGGAGGTGT CGTACCGCGT TCTACGCCAC CTTGCGCAGC
851 CCGGCGGCGG CTCTGACATG GCTACACCAT TAGGCCCTGC CAGCTCCCTG
901 CCCCAGAGCT TCCTGCTCAA GTCTTTAGAG CAAGTGAGGA AGATCCAGGG
951 CGATGGCGCA GCGCTCCAGG AGAAGCTGTG TGCCACCTAA TAA;
(SEQ ID NO:155)

pMON15982

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pMON15966

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PMON32132

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PMON32133

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751

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851 GCCTTTCCT CTACCAGGGG CTCCTGCAGG CCCTGGAAGG GATATCCCCC
901 GAGTTGGGTC CCACCTTGGA CACACTGCAG CTGGACGTCG CCGACTTTGC
951 CACCACCATC TGGCAGCAGA TGGAA (SEQ ID NO:268)
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pmon16027.seq

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     351
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     401
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     651
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         AGAAGCTGTG TGCCACCTAC AAGCTGTGCC ACCCCGAGGA GCTGGTGCTG
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     801
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pmon16028.seq

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     651
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10. 101 151 201 251 301 15 351 401 451	GGTCCGTCTC CTCCACAGG AGCTTCCAAC AGGGTCCACC CGCCGCCTGC CATGTCCTTC TACACCTGTC CCCAGATGA	CCACTTGCCT CTCCTTGGGG CAGGACCACA ACCTGCTCCG CTCGCCGTCA TGCTGACCTC ACAGCAGACT CTGCTGCCTG GGAGACCAAG GAGTGATGGC	CCCTGCAGAG GCTCACAAGG AGGAAAGGTG GGGAATTCGG CGAGTCCTCA GAGCCAGTGC CTGTGGACTT GCACAGGACA	CCTCCTTGGA ATCCCAATGC CGTTTCCTGA CGGCAACATG GTAAACTGCT CCAGAGGTTC TAGCTTGGGA TTCTGGGAAGC	ACCCAGCTTC CATCTTCCTG TGCTTGTAGG GCGTCTCCGG TCGTGACTCC ACCCTTTGCC GAATGGAAAA
431	(SEQ ID NO:2		AGCACGGGGA	CAACIG	
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201 25 251 301 351 401 451	CACCTGTCCT CAGATGGAGG GCTGGAGGGA CATCCCTCCT	AGACCAAGGC GTGATGGCAG GGGGCAGCTT TCCTTGGAAC	GTGGACTTTA ACAGGACATT CACGGGGACA TCTGGACAGG	GCTTGGGAGA CTGGGAGCAG ACTGGGACCC TCCGTCTCCT	ATGGAAAACC TGACCCTTCT ACTTGCCTCT

TABLE 3 PROTEIN SEQUENCES

5 pMON26458pep

SerProAlaProProAlaCysAspLeuArgValLeuSerLysLeuLeuArgAspSerHis ValLeuHisSerArgLeuSerGlnCysProGluValHisProLeuProThrProValLeu LeuProAlaValAspPheSerLeuGlyGluTrpLysThrGlnMetGluGluThrLysAla GlnAspIleLeuGlyAlaValThrLeuLeuLeuGluGlyValMetAlaAlaArgGlyGln LeuGlyProThrCysLeuSerSerLeuLeuGlyGlnLeuSerGlyGlnValArgLeuLeu LeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnLeuProProGlnGlyArgThrThrAla HisLysAspProAsnAlaIlePheLeuSerPheGlnHisLeuLeuArgGlyLysValArg PheLeuMetLeuValGlyGlySerThrLeuCysValArgGluPhe

15 (SEQ ID NO:161)

pMON28548pep

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pMON28500

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- ValThrLeuLeuGluGlyValMetAlaAlaArgGlyGlnLeuGlyProThrCysLeuSe rSer
 - LeuLeuGlyGlnLeuSerGlyGlnValArgLeuLeuGlyAlaLeuGlnSerLeuLeuGlyThr

GlnLeuProProGlnGlyArgThrThrAlaHisLysAspProAsnAlaIlePheLeuSerPheGln

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- 5 PheGlyAsnMetAlaSerProAlaProProAlaCysAspLeuArgValLeuSerLysLeuLe uArg
 - AspSerHisValLeuHisSerArgLeuSerGlnCysProGluValHisProLeuProThrProVal
 - LeuLeuProAlaValAspPheSerLeuGlyGluTrpLysThrGlnMetGluGluThrLysAl
 - AspIleLeuGlyAlaValThrLeuLeuGluGlyValMetAlaAlaArgGlyGlnLeuGlyPro
 - $\label{thm:cysleu} Thr \texttt{CysLeuSerSerLeuLeuGlyGlnLeuSerGlyGlnValArgLeuLeuGlyAlaLeuGln} \\$
- 15 SerLeuLeuGlyThrGlnLeuProProGlnGlyArgThrThrAlaHisLysAspProAsnAl alle
 - PheLeuSerPheGlnHisLeuLeuArgGlyLysValArgPheLeuMetLeuValGlyGlySerThr
 - LeuCysValArg (SEQ ID NO:163)

20

10

pMON28501

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40 pMON28502

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(SEQ ID NO:165)

13182.Pept

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13183.Pept

Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu 10 Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Ser Gly Gly Ser Gly Gly Ser Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr (SEQ ID NO:167) 15

13184.Pept

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13185.Pept

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Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu
Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile

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Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr
    Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp
    Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu
    Gln Ala Gln Glu Gln Tyr Val Glu Gly Gly Gly Ser Pro
    Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro
    Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Pro Glu Leu Gly
    Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr
    Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu
    Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln
10
   Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe
    Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Ser
    Gly Gly Ser Gly Ser Gln Ser Phe Leu Leu Lys Ser Leu Glu
    Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys
    Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu
15
   Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys
    Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
    Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly
    Ile Ser (SEQ ID NO:169)
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20 13186.Pept

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    Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile
    Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr
    Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp
    Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu
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   Gln Ala Gln Glu Gln Gln Tyr Val Glu Gly Gly Gly Ser Pro
    Gly Gly Gly Ser Gly Gly Ser Asn Met Ala Met Ala Pro Ala
    Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe
    Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
    Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
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    Ser Gly Gly Ser Gly Ser Gln Ser Phe Leu Leu Lys Ser Leu
    Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu
    Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val
    Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu
40
   His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu
    Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu
    Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu
    Leu Gly (SEQ ID NO:170)
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13187.Pept

45

Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arq Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln Tyr Val Glu Gly Gly Gly Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro 10 Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Ser Gly Gly Ser Gly Ser Gln Ser Phe Leu Leu Lys Ser Leu 15 Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu 20 Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly (SEQ ID NO:171)

25 13188. Pept

Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu 30 Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Tyr Val Glu Gly Gly Gly Ser Pro 35 Gly Gly Gly Ser Gly Gly Ser Asn Met Ala Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Ser Gly Gly Ser Gly Gly Ser Gln Ser Phe Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln 40 Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr 45 Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro (SEQ ID NO:172)

13189.Pept

Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr 10 Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Tyr Val Glu Gly Gly Gly Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Gln Gly Ala 15 Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Ser Gly Gly Ser Gly Gly Ser Gln Ser Phe Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys 20 Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr 25 Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro (SEQ ID NO:173)

13190.Pept

30 Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile 35 Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln Tyr Val Glu Gly Gly Gly Ser Pro Gly Gly Gly Ser Gly Gly Ser Asn Met Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe 40 Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Ser Gly Gly Ser Gly Ser Gln Ser Phe Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu 45 Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala (SEQ ID NO:174)

5

13191.Pept

Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arq 10 Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu 15 Gln Ala Gln Glu Gln Gln Tyr Val Glu Gly Gly Gly Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe 20 Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Ser Gly Gly Ser Gly Ser Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys 25 Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 30 Phe Ala (SEQ ID NO:175)

13192.Pept

35 Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arq Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arq Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr 40 Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Tyr Val Glu Gly Gly Gly Ser Pro Gly Gly Gly Ser Gly Gly Ser Asn Met Ala Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Gly His Ser Leu Gly Ile Pro 45 Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr (SEQ ID NO:176)

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13193.Pept

Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp 15 Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu 20 Gln Ala Gln Glu Gln Gln Tyr Val Glu Gly Gly Gly Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala 25 Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg 30 Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr (SEQ ID NO:177)

35

25190.Pept

Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg
40 Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp
Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu
Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile
Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr
Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp
Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu
Gln Ala Gln Glu Gln Gln Tyr Val Glu Gly Gly Gly Ser Pro
Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Pro Glu Leu Gly

Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Glu Glu Glu Glu Glu Gly Gly Ile Ser (SEQ ID NO:178)

15 pMON25191.Pep

Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu 20 Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Gln Gln Tyr Val Glu Gly Gly Gly Ser Pro 25 Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln 30 Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu 35 Leu Val Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser (SEQ ID NO:179)

13194.Pept

40

Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr

Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln Tyr Val Glu Gly Gly Gly Ser Pro Gly Gly Gly Ser Gly Gly Ser Asn Met Ala Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala 10 Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr 15 Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly (SEQ ID NO:180)

13195.Pept

20 Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile 25 Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Tyr Val Glu Gly Gly Gly Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro 30 Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu 35 Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln 40 Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly (SEQ ID NO:181)

45 13196. Pept

Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg

Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Tyr Val Glu Gly Gly Gly Ser Pro Gly Gly Gly Ser Gly Gly Ser Asn Met Ala Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg 10 Val Leu Arg His Leu Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His 15 Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala 20 Pro Ala Leu Gln Pro (SEQ ID NO:182)

13197.Pept

25 Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp 30 Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln Tyr Val Glu Gly Gly Gly Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Gln Gly Ala 35 Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arq Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala 40 Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp 45 Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro (SEQ ID NO:183)

13198.Pept

Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg 5 Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp 10 Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Tyr Val Glu Gly Gly Gly Ser Pro Gly Gly Gly Ser Gly Gly Ser Asn Met Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Lys 15 Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 20 Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala (SEQ ID NO:184)

13199. Pept

25

30 Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Tyr Val Glu Gly Gly Gly Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Ser Ala Phe Gln 40 Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu 45 Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala (SEQ ID NO:185)

5

31104.Pep

Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met 10 Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln 15 Gln Gly Gly Ser Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Tyr Val Glu Gly Gly Gly Gly Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg 20 Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Ser Gly Gly Ser Gly Gly Ser Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly 25 His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met 30 Ala Pro Ala Leu Gln Pro (SEQ ID NO:186)

31105.Pep

35 Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln Gly Gly Ser Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg 40 Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Tyr Val Glu Gly Gly Gly Gly Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala 45 Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Ser Gly Gly

Ser Gly Gly Ser Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro (SEQ ID NO:187)

10

31106.Pep

Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln 15 Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gly Gly Gly Ser Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val 20 Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Tyr Val Glu Gly Gly Gly Gly Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg 25 Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Ser Gly Gly Ser Gly Gly Ser Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser 30 Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met 35 Ala Pro Ala Leu Gln Pro (SEQ ID NO:188)

31107.Pep

40 Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln Gly Gly Gly Ser Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Tyr Val Glu Gly Gly

Gly Gly Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Ser Gly Gly Ser Gly Gly Ser Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gly Gln Ala Leu Gln Ala Leu Gln Glu Leu Val Leu Leu Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro (SEQ ID NO:189)

15

31108.Pep

Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met 20 Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln 25 Gln Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Tyr Val Glu Gly Gly Gly Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Gln Gly Ala Met Pro Ala 30 Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Ser Gly Gly Ser Gly Gly Ser Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His 35 Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp 40 Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro (SEQ ID NO:190)

31109. Pep

45 Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr

Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Ser Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Tyr Val Glu Gly Gly Gly Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala 10 Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Ser Gly Gly Ser Gly Gly Ser Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp 15 Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro 20 (SEQ ID NO:191)

31110.Pep

Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln 25 Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn 30 Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Tyr Val Glu Gly Gly Gly Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Gln Gly Ala Met Pro Ala 35 Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Ser Gly Gly Ser Gly Gly Ser Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His 40 Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp 45 Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro (SEQ ID NO:192)

31111. Pep

Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Ser Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln 10 Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Tyr Val Glu Gly Gly Gly Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg 15 His Leu Ala Gln Pro Ser Gly Gly Ser Gly Gly Ser Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp 20 Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro 25 (SEO ID NO:193)

pMON15981

MetAlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAla 30 ${\tt ProLeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsn}$ LeuArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSer GlyIleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaPro SerArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThr PheTyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGly 35 SerProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGlu SerHisLysSerProAsnMetAlaTyrLysLeuCysHisProGluGluLeuValLeuLeu GlyHisSerLeuGlyIleProTrpAlaProLeuSerSerCysProSerGlnAlaLeuGln LeuAlaGlyCysLeuSerGlnLeuHisSerGlyLeuPheLeuTyrGlnGlyLeuLeuGln AlaLeuGluGlyIleSerProGluLeuGlyProThrLeuAspThrLeuGlnLeuAspVal 40 AlaAspPheAlaThrThrIleTrpGlnGlnMetGluGluLeuGlyMetAlaProAlaLeu GlnProThrGlnGlyAlaMetProAlaPheAlaSerAlaPheGlnArqArqAlaGlyGly ValLeuValAlaSerHisLeuGlnSerPheLeuGluValSerTyrArgValLeuArgHis LeuAlaGlnProGlyGlyGlySerAspMetAlaThrProLeuGlyProAlaSerSerLeu ProGlnSerPheLeuLeuLysSerLeuGluGlnValArgLysIleGlnGlyAspGlyAla 45 AlaLeuGlnGluLysLeuCysAlaThr (SEQ ID NO:194)

MetAlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAla ProLeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsn LeuArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSer 5 GlyIleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaPro SerArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThr PheTyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGly SerProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGlu SerHisLysSerProAsnMetAlaProGluLeuGlyProThrLeuAspThrLeuGlnLeu 10 AspValAlaAspPheAlaThrThrIleTrpGlnGlnMetGluGluLeuGlyMetAlaPro AlaLeuGlnProThrGlnGlyAlaMetProAlaPheAlaSerAlaPheGlnArgArgAla GlyGlyValLeuValAlaSerHisLeuGlnSerPheLeuGluValSerTyrArqValLeu ArgHisLeuAlaGlnProGlyGlyGlySerAspMetAlaThrProLeuGlyProAlaSer SerLeuProGlnSerPheLeuLeuLysSerLeuGluGlnValArgLysIleGlnGlyAsp 15 GlyAlaAlaLeuGlnGluLysLeuCysAlaThrTyrLysLeuCysHisProGluGluLeu ValLeuLeuGlyHisSerLeuGlyIleProTrpAlaProLeuSerSerCysProSerGln AlaLeuGlnLeuAlaGlyCysLeuSerGlnLeuHisSerGlyLeuPheLeuTyrGlnGly LeuLeuGlnAlaLeuGluGlyIleSer (SEQ ID NO:195)

20 pMON15965

MetAlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAla ProLeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsn GlvIleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaPro 25 SerArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThr PheTyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGly SerProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGlu SerHisLysSerProAsnMetAlaSerAlaPheGlnArqArqAlaGlyGlyValLeuVal 30 AlaSerHisLeuGlnSerPheLeuGluValSerTyrArqValLeuArqHisLeuAlaGln ProGlyGlyGlySerAspMetAlaThrProLeuGlyProAlaSerSerLeuProGlnSer PheLeuLeuLysSerLeuGluGlnValArqLysIleGlnGlyAspGlyAlaAlaLeuGln GluLysLeuCysAlaThrTyrLysLeuCysHisProGluGluLeuValLeuLeuGlyHis SerLeuGlyIleProTrpAlaProLeuSerSerCysProSerGlnAlaLeuGlnLeuAla 35 GlyCysLeuSerGlnLeuHisSerGlyLeuPheLeuTyrGlnGlyLeuLeuGlnAlaLeu GluGlyIleSerProGluLeuGlyProThrLeuAspThrLeuGlnLeuAspValAlaAsp PheAlaThrThrIleTrpGlnGlnMetGluGluLeuGlyMetAlaProAlaLeuGlnPro ThrGlnGlyAlaMetProAlaPheAla (SEQ ID NO:196)

40 pMON15966

MetAlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAla ProLeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsn LeuArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSer GlyIleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaPro SerArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThr PheTyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGly SerProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGlu SerHisLysSerProAsnMetAlaMetAlaProAlaLeuGlnProThrGlnGlyAlaMet ProAlaPheAlaSerAlaPheGlnArgArgAlaGlyGlyValLeuValAlaSerHisLeu GlnSerPheLeuGluValSerTyrArgValLeuArgHisLeuAlaGlnProGlyGlyGly SerAspMetAlaThrProLeuGlyProAlaSerSerLeuProGlnSerPheLeuLeuLys SerLeuGluGlnValArgLysIleGlnGlyAspGlyAlaAlaLeuGlnGluLysLeuCys AlaThrTyrLysLeuCysHisProGluGluLeuValLeuLeuGlyHisSerLeuGlyIle ProTrpAlaProLeuSerSerCysProSerGlnAlaLeuGlnLeuAlaGlyCysLeuSer GlnLeuHisSerGlyLeuPheLeuTyrGlnGlyLeuLeuGlnAlaLeuGluGlyIleSer ProGluLeuGlyProThrLeuAspThrLeuGlnLeuAspValAlaAspPheAlaThrThr IleTrpGlnGlnMetGluGluLeuGly (SEQ ID NO:197)

pMON15967

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15 MetAlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAla ProLeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsn LeuArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSer GlyIleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaPro SerArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThr 20 PheTyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGly SerProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGlu SerHisLysSerProAsnMetAlaThrGlnGlyAlaMetProAlaPheAlaSerAlaPhe GlnArgArgAlaGlyGlyValLeuValAlaSerHisLeuGlnSerPheLeuGluValSer TyrArgValLeuArgHisLeuAlaGlnProGlyGlyGlySerAspMetAlaThrProLeu 25 GlyProAlaSerSerLeuProGlnSerPheLeuLeuLysSerLeuGluGlnValArgLys IleGlnGlyAspGlyAlaAlaLeuGlnGluLysLeuCysAlaThrTyrLysLeuCysHis ProGluGluLeuValLeuLeuGlyHisSerLeuGlyIleProTrpAlaProLeuSerSer CysProSerGlnAlaLeuGlnLeuAlaGlyCysLeuSerGlnLeuHisSerGlyLeuPhe LeuTyrGlnGlyLeuLeuGlnAlaLeuGluGlyIleSerProGluLeuGlyProThrLeu 30 AspThrLeuGlnLeuAspValAlaAspPheAlaThrThrIleTrpGlnGlnMetGluGlu LeuGlyMetAlaProAlaLeuGlnPro (SEQ ID NO:198)

pMON31112.pep

MetAlaAsnCysSerAsnMetIleAspGluIleIleThrHisLeuLysGlnProProLeu
ProLeuLeuAspPheAsnAsnLeuAsnGlyGluAspGlnAspIleLeuMetAspAsnAsn
LeuArgArgProAsnLeuGluAlaPheAsnArgAlaValLysSerLeuGlnAsnAlaSer
AlaIleGluSerIleLeuLysAsnLeuLeuProCysLeuProLeuAlaThrAlaAlaPro
40 ThrArgHisProIleHisIleLysAspGlyAspTrpAsnGluPheArgArgLysLeuThr
PheTyrLeuLysThrLeuGluAsnAlaGlnAlaGlnGlnTyrValGluGlyGlyGlyGly
SerProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGlu
SerHisLysSerProAsnMetAlaThrGlnGlyAlaMetProAlaPheAlaSerAlaPhe
GlnArgArgAlaGlyGlyValLeuValAlaSerHisLeuGlnSerPheLeuGluValSer
45 TyrArgValLeuArgHisLeuAlaGlnProSerGlyGlySerGlyGlySerGlnSerPhe
LeuLeuLysSerLeuGluGlnValArgLysIleGlnGlyAspGlyAlaAlaLeuGlnGlu
LysLeuCysAlaThrTyrLysLeuCysHisProGluGluLeuValLeuLeuGlyHisSer

LeuGlyIleProTrpAlaProLeuSerSerCysProSerGlnAlaLeuGlnLeuAlaGlyCysLeuSerGlnLeuHisSerGlyLeuPheLeuTyrGlnGlyLeuLeuGlnAlaLeuGluGlyIleSerProGluLeuGlyProThrLeuAspThrLeuGlnLeuAspValAlaAspPheAlaThrThrIleTrpGlnGlnMetGluGluLeuGlyMetAlaProAlaLeuGlnPro(SEQ ID NO:199)

pMON31113.pep

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10 MetAlaAsnCysSerAsnMetIleAspGluIleIleThrHisLeuLysGlnProProLeu ${\tt ProLeuLeuAspPheAsnAsnLeuAsnGlyGluAspGlnAspIleLeuMetGluAsnAsn}$ LeuArqArqProAsnLeuGluAlaPheAsnArqAlaValLysSerLeuGlnAsnAlaSer AlaIleGluSerIleLeuLysAsnLeuLeuProCysLeuProLeuAlaThrAlaAlaPro ThrArgHisProIleIleIleArgAspGlyAspTrpAsnGluPheArgArgLysLeuThr 15 PheTyrLeuLysThrLeuGluAsnAlaGlnAlaGlnGlnTyrValGluGlyGlyGlyGly SerProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGlu ${\tt SerHisLysSerProAsnMetAlaThrGlnGlyAlaMetProAlaPheAlaSerAlaPhe}$ GlnArqArqAlaGlyGlyValLeuValAlaSerHisLeuGlnSerPheLeuGluValSer TyrArqValLeuArqHisLeuAlaGlnProThrProLeuGlyProAlaSerSerLeuPro 20 GlnSerPheLeuLeuLysSerLeuGluGlnValArgLysIleGlnGlyAspGlyAlaAla LeuGlnGluLysLeuCysAlaThrTyrLysLeuCysHisProGluGluLeuValLeuLeu GlyHisSerLeuGlyIleProTrpAlaProLeuSerSerCysProSerGlnAlaLeuGln LeuAlaGlyCysLeuSerGlnLeuHisSerGlyLeuPheLeuTyrGlnGlyLeuLeuGln AlaLeuGluGlyIleSerProGluLeuGlyProThrLeuAspThrLeuGlnLeuAspVal 25 AlaAspPheAlaThrThrIleTrpGlnGlnMetGluGluLeuGlyMetAlaProAlaLeu (SEQ ID NO:200) GlnPro

pMON31114.pep

30 MetAlaAsnCysSerAsnMetIleAspGluIleIleThrHisLeuLysGlnProProLeu ProLeuLeuAspPheAsnAsnLeuAsnGlyGluAspGlnAspIleLeuMetGluAsnAsn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser LeuAlaIleGluSerIleLeuLysAsnLeuLeuProCysLeuProLeuAlaThrAlaAlaPro 35 $Thr \verb|ArgHisProIleIleIleArgAspGlyAspTrpAsnGluPheArgArgLysLeuThr|$ PheTyrLeuLysThrLeuGluAsnAlaGlnAlaGlnGlnTyrValGluGlyGlyGlyGly SerProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGlu SerHisLysSerProAsnMetAlaThrGlnGlyAlaMetProAlaPheAlaSerAlaPhe GlnArqArqAlaGlyGlyValLeuValAlaSerHisLeuGlnSerPheLeuGluValSer 40 TyrArgValLeuArgHisLeuAlaGlnProSerGlyGlySerGlyGlySerGlnSerPhe LeuLeuLysSerLeuGluGlnValArqLysIleGlnGlyAspGlyAlaAlaLeuGlnGlu LysLeuCysAlaThrTyrLysLeuCysHisProGluGluLeuValLeuLeuGlyHisSer LeuGlyIleProTrpAlaProLeuSerSerCysProSerGlnAlaLeuGlnLeuAlaGly CysLeuSerGlnLeuHisSerGlyLeuPheLeuTyrGlnGlyLeuLeuGlnAlaLeuGlu 45 GlyIleSerProGluLeuGlyProThrLeuAspThrLeuGlnLeuAspValAlaAspPhe AlaThrThrIleTrpGlnGlnMetGluGluLeuGlyMetAlaProAlaLeuGlnPro (SEQ ID NO:201)

pMON31115.pep

5 ${\tt MetAlaAsnCysSerAsnMetIleAspGluIleIleThrHisLeuLysGlnProProLeu}$ ProLeuLeuAspPheAsnAsnLeuAsnGlyGluAspGlnAspIleLeuMetAspAsnAsn LeuArgArgProAsnLeuGluAlaPheAsnArgAlaValLysSerLeuGlnAsnAlaSer AlaIleGluSerIleLeuLysAsnLeuLeuProCysLeuProLeuAlaThrAlaAlaPro ThrArgHisProIleHisIleLysAspGlyAspTrpAsnGluPheArgArgLysLeuThr 10 PheTyrLeuLysThrLeuGluAsnAlaGlnAlaGlnGlnTyrValGluGlyGlyGlyGly SerProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGlu SerHisLysSerProAsnMetAlaThrGlnGlyAlaMetProAlaPheAlaSerAlaPhe GlnArgArgAlaGlyGlyValLeuValAlaSerHisLeuGlnSerPheLeuGluValSer TyrArgValLeuArgHisLeuAlaGlnProThrProLeuGlyProAlaSerSerLeuPro 15 GlnSerPheLeuLeuLysSerLeuGluGlnValArgLysIleGlnGlyAspGlyAlaAla LeuGlnGluLysLeuCysAlaThrTyrLysLeuCysHisProGluGluLeuValLeuLeu GlyHisSerLeuGlyIleProTrpAlaProLeuSerSerCysProSerGlnAlaLeuGln LeuAlaGlyCysLeuSerGlnLeuHisSerGlyLeuPheLeuTyrGlnGlyLeuLeuGln AlaLeuGluGlyIleSerProGluLeuGlyProThrLeuAspThrLeuGlnLeuAspVal 20 AlaAspPheAlaThrThrIleTrpGlnGlnMetGluGluLeuGlyMetAlaProAlaLeu GlnPro (SEQ ID NO:202)

pMON28505

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AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly IleGluAlaIleLeuArqAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer 30 ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlySer ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer HisLysSerProAsnMetGluValHisProLeuProThrProValLeuLeuProAlaVal AspPheSerLeuGlyGluTrpLysThrGlnMetGluGluThrLysAlaGlnAspIleLeu 35 GlyAlaValThrLeuLeuGluGlyValMetAlaAlaArqGlyGlnLeuGlyProThr CysLeuSerSerLeuLeuGlyGlnLeuSerGlyGlnValArqLeuLeuGlyAlaLeu GlnSerLeuLeuGlyThrGlnLeuProProGlnGlyArqThrThrAlaHisLysAspPro AsnAlaIlePheLeuSerPheGlnHisLeuLeuArgGlyLysValArgPheLeuMetLeu ValGlyGlySerThrLeuCysValArgGluPheGlyGlyAsnMetAlaSerProAlaPro 40 ProAlaCysAspLeuArgValLeuSerLysLeuLeuArgAspSerHisValLeuHisSer ArgLeuSerGlnCysPro (SEQ ID NO:203)

pMON28506

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45 AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly IleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer HisLysSerProAsnMetLeuProThrProValLeuLeuProAlaValAspPheSerLeu GlyGluTrpLysThrGlnMetGluGluThrLysAlaGlnAspIleLeuGlyAlaValThr LeuLeuGluGlyValMetAlaAlaArgGlyGlnLeuGlyProThrCysLeuSerSer LeuLeuGlyGlnLeuSerGlyGlnValArgLeuLeuLeuGlyAlaLeuGlnSerLeuLeu GlyThrGlnLeuProProGlnGlyArgThrThrAlaHisLysAspProAsnAlaIlePhe LeuSerPheGlnHisLeuLeuArgGlyLysValArgPheLeuMetLeuValGlyGlySer ThrLeuCysValArgGluPheGlyGlyAsnMetAlaSerProAlaProProAlaCysAsp LeuArgValLeuSerLysLeuLeuArgAspSerHisValLeuHisSerArgLeuSerGln CysProGluValHisPro (SEQ ID NO: 204)

15 pMON28507

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AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArqAsnLeu ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly 20 IleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlySer ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer HisLysSerProAsnMetValLeuLeuProAlaValAspPheSerLeuGlyGluTrpLys 25 ThrGlnMetGluGluThrLysAlaGlnAspIleLeuGlyAlaValThrLeuLeuGlu GlyValMetAlaAlaArqGlyGlnLeuGlyProThrCysLeuSerSerLeuLeuGlyGln LeuSerGlyGlnValArgLeuLeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnLeu ProProGlnGlyArqThrThrAlaHisLysAspProAsnAlaIlePheLeuSerPheGln HisLeuLeuArgGlyLysValArgPheLeuMetLeuValGlyGlySerThrLeuCysVal 30 ArgGluPheGlyGlyAsnMetAlaSerProAlaProProAlaCysAspLeuArgValLeu SerLysLeuLeuArgAspSerHisValLeuHisSerArgLeuSerGlnCysProGluVal HisProLeuProThrPro (SEQ ID NO:205)

pMON28508

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AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro
LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu
ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly
IleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer
40 ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe
TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer
ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer
HisLysSerProAsnMetAlaValAspPheSerLeuGlyGluTrpLysThrGlnMetGlu
GluThrLysAlaGlnAspIleLeuGlyAlaValThrLeuLeuLeuGluGlyValMetAla
45 AlaArgGlyGlnLeuGlyProThrCysLeuSerSerLeuLeuGlyGlnLeuSerGlyGln
ValArgLeuLeuLeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnLeuProProGlnGly
ArgThrThrAlaHisLysAspProAsnAlaIlePheLeuSerPheGlnHisLeuLeuArg

GlyLysValArgPheLeuMetLeuValGlyGlySerThrLeuCysValArgGluPheGlyGlyAsnMetAlaSerProAlaProProAlaCysAspLeuArgValLeuSerLysLeuLeuArgAspSerHisValLeuHisSerArgLeuSerGlnCysProGluValHisProLeuProThrProValLeuLeuPro (SEQ ID NO:206)

pMON28509

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AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu 10 ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly ${\tt IleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer}$ ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer 15 HisLysSerProAsnMetAspPheSerLeuGlyGluTrpLysThrGlnMetGluGluThr LysAlaGlnAspIleLeuGlyAlaValThrLeuLeuGluGlyValMetAlaAlaArg GlyGlnLeuGlyProThrCysLeuSerSerLeuLeuGlyGlnLeuSerGlyGlnValArg LeuLeuLeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnLeuProProGlnGlyArgThr ThrAlaHisLysAspProAsnAlaIlePheLeuSerPheGlnHisLeuLeuArgGlyLys 20 ValArgPheLeuMetLeuValGlyGlySerThrLeuCysValArgGluPheGlyGlyAsn MetAlaSerProAlaProProAlaCysAspLeuArgValLeuSerLysLeuLeuArgAsp SerHisValLeuHisSerArqLeuSerGlnCysProGluValHisProLeuProThrPro ValLeuLeuProAlaVal (SEQ ID NO:207)

25 pMON28510

AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly 30 ${\tt IleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer}$ ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer HisLysSerProAsnMetGlyGluTrpLysThrGlnMetGluGluThrLysAlaGlnAsp 35 IleLeuGlyAlaValThrLeuLeuGluGlyValMetAlaAlaArqGlyGlnLeuGly ProThrCysLeuSerSerLeuLeuGlyGlnLeuSerGlyGlnValArqLeuLeuGly AlaLeuGlnSerLeuLeuGlyThrGlnLeuProProGlnGlyArgThrThrAlaHisLys AspProAsnAlaIlePheLeuSerPheGlnHisLeuLeuArgGlyLysValArgPheLeu MetLeuValGlyGlySerThrLeuCysValArgGluPheGlyGlyAsnMetAlaSerPro 40 AlaProProAlaCysAspLeuArgValLeuSerLysLeuLeuArgAspSerHisValLeu HisSerArgLeuSerGlnCysProGluValHisProLeuProThrProValLeuLeuPro AlaValAspPheSerLeu (SEQ ID NO:208)

pMON28511

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AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaProLeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu

ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly IleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer HisLysSerProAsnMetGlyProThrCysLeuSerSerLeuLeuGlyGlnLeuSerGly GlnValArgLeuLeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnLeuProProGln GlyArgThrThrAlaHisLysAspProAsnAlaIlePheLeuSerPheGlnHisLeuLeu ArgGlyLysValArgPheLeuMetLeuValGlyGlySerThrLeuCysValArgGluPhe GlyGlyAsnMetAlaSerProAlaProProAlaCysAspLeuArgValLeuSerLysLeu LeuArgAspSerHisValLeuHisSerArgLeuSerGlnCysProGluValHisProLeu ProThrProValLeuLeuProAlaValAspPheSerLeuGlyGluTrpLysThrGlnMet GluGluThrLysAlaGlnAspIleLeuGlyAlaValThrLeuLeuLeuGluGlyValMet AlaAlaArgGlyGlnLeu (SEQ ID NO:209)

15 pMON28512

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AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArqAsnLeu 20 ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly ${\tt IleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer}$ ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer 25 HisLysSerProAsnMetGlyThrGlnLeuProProGlnGlyArgThrThrAlaHisLys AspProAsnAlaIlePheLeuSerPheGlnHisLeuLeuArgGlyLysValArgPheLeu MetLeuValGlyGlySerThrLeuCysValArgGluPheGlyGlyAsnMetAlaSerPro AlaProProAlaCysAspLeuArqValLeuSerLysLeuLeuArqAspSerHisValLeu HisSerArgLeuSerGlnCysProGluValHisProLeuProThrProValLeuLeuPro 30 AlaValAspPheSerLeuGlyGluTrpLysThrGlnMetGluGluThrLysAlaGlnAsp IleLeuGlyAlaValThrLeuLeuLeuGluGlyValMetAlaAlaArgGlyGlnLeuGly ProThrCysLeuSerSerLeuLeuGlyGlnLeuSerGlyGlnValArqLeuLeuGly AlaLeuGlnSerLeuLeu (SEQ ID NO:210)

35 pMON28513

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AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro
LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu
ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly
IleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer
ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe
TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer
ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer
HisLysSerProAsnMetGlyArgThrThrAlaHisLysAspProAsnAlaIlePheLeu
SerPheGlnHisLeuLeuArgGlyLysValArgPheLeuMetLeuValGlyGlySerThr
LeuCysValArgGluPheGlyGlyAsnMetAlaSerProAlaProProAlaCysAspLeu
ArgValLeuSerLysLeuLeuArgAspSerHisValLeuHisSerArgLeuSerGlnCys

ProGluValHisProLeuProThrProValLeuLeuProAlaValAspPheSerLeuGlyGluTrpLysThrGlnMetGluGluThrLysAlaGlnAspIleLeuGlyAlaValThrLeuLeuGluGlyValMetAlaAlaArgGlyGlnLeuGlyProThrCysLeuSerSerLeuLeuGlyGlnLeuSerGlyGlnValArgLeuLeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnLeuProProGln (SEQ ID NO:211)

pMON28514

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AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArqProProAlaPro 10 LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArqAsnLeu ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly IleGluAlaIleLeuArqAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlySer 15 ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer HisLysSerProAsnMetAlaHisLysAspProAsnAlaIlePheLeuSerPheGlnHis LeuLeuArgGlyLysValArgPheLeuMetLeuValGlyGlySerThrLeuCysValArg GluPheGlyGlyAsnMetAlaSerProAlaProProAlaCysAspLeuArgValLeuSer LysLeuLeuArgAspSerHisValLeuHisSerArgLeuSerGlnCysProGluValHis 20 ProLeuProThrProValLeuLeuProAlaValAspPheSerLeuGlyGluTrpLysThr GlnMetGluGluThrLysAlaGlnAspIleLeuGlyAlaValThrLeuLeuGluGly ValMetAlaAlaArgGlyGlnLeuGlyProThrCysLeuSerSerLeuLeuGlyGlnLeu SerGlyGlnValArgLeuLeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnLeuPro ProGlnGlyArgThrThr (SEQ ID NO:212)

pMON28515

AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu 30 ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly IleGluAlaIleLeuArqAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer 35 HisLysSerProAsnMetAspProAsnAlaIlePheLeuSerPheGlnHisLeuLeuArg GlyLysValArgPheLeuMetLeuValGlyGlySerThrLeuCysValArgGluPheGly GlyAsnMetAlaSerProAlaProProAlaCysAspLeuArgValLeuSerLysLeuLeu ArgAspSerHisValLeuHisSerArgLeuSerGlnCysProGluValHisProLeuPro ThrProValLeuLeuProAlaValAspPheSerLeuGlyGluTrpLysThrGlnMetGlu 40 GluThrLysAlaGlnAspIleLeuGlyAlaValThrLeuLeuGluGlyValMetAla AlaArgGlyGlnLeuGlyProThrCysLeuSerSerLeuLeuGlyGlnLeuSerGlyGln ValArgLeuLeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnLeuProProGlnGly ArgThrThrAlaHisLys (SEQ ID NO:213)

45 pMON28516

AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro

LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly IleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe 5 TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlySer ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer HisLysSerProAsnMetAlaIlePheLeuSerPheGlnHisLeuLeuArgGlyLysVal ArgPheLeuMetLeuValGlyGlySerThrLeuCysValArgGluPheGlyGlyAsnMet AlaSerProAlaProProAlaCysAspLeuArgValLeuSerLysLeuLeuArgAspSer 10 HisValLeuHisSerArgLeuSerGlnCysProGluValHisProLeuProThrProVal LeuLeuProAlaValAspPheSerLeuGlyGluTrpLysThrGlnMetGluGluThrLys AlaGlnAspIleLeuGlyAlaValThrLeuLeuLeuGluGlyValMetAlaAlaArgGly GlnLeuGlyProThrCysLeuSerSerLeuLeuGlyGlnLeuSerGlyGlnValArgLeu LeuLeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnLeuProProGlnGlyArgThrThr 15 AlaHisLysAspProAsn (SEQ ID NO:214)

pMON28519

AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArqProProAlaPro 20 ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly IleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer 25 ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer HisLysSerProAsnMetGluValHisProLeuProThrProValLeuLeuProAlaVal AspPheSerLeuGlyGluTrpLysThrGlnMetGluGluThrLysAlaGlnAspIleLeu GlyAlaValThrLeuLeuGluGlyValMetAlaAlaArgGlyGlnLeuGlyProThr CysLeuSerSerLeuLeuGlyGlnLeuSerGlyGlnValArgLeuLeuLeuGlyAlaLeu 30 GlnSerLeuLeuGlyThrGlnLeuProProGlnGlyArgThrThrAlaHisLysAspPro AsnAlaIlePheLeuSerPheGlnHisLeuLeuArgGlyLysValArgPheLeuMetLeu ValGlyGlySerThrLeuCysValArgGluPheGlyAsnMetAlaSerProAlaProPro AlaCysAspLeuArgValLeuSerLysLeuLeuArgAspSerHisValLeuHisSerArg LeuSerGlnCysPro (SEQ ID NO:215)

pMON28520

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AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro
LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu
40 ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly
IleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer
ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe
TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer
ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer
45 HisLysSerProAsnMetLeuProThrProValLeuLeuProAlaValAspPheSerLeu
GlyGluTrpLysThrGlnMetGluGluThrLysAlaGlnAspIleLeuGlyAlaValThr
LeuLeuLeuGluGlyValMetAlaAlaArqGlyGlnLeuGlyProThrCysLeuSerSer

LeuLeuGlyGlnLeuSerGlyGlnValArgLeuLeuGlyAlaLeuGlnSerLeuLeu GlyThrGlnLeuProProGlnGlyArgThrThrAlaHisLysAspProAsnAlaIlePhe LeuSerPheGlnHisLeuLeuArgGlyLysValArgPheLeuMetLeuValGlyGlySer ThrLeuCysValArgGluPheGlyAsnMetAlaSerProAlaProProAlaCysAspLeu ArgValLeuSerLysLeuLeuArgAspSerHisValLeuHisSerArgLeuSerGlnCys ProGluValHisPro (SEQ ID NO:216)

pMON28521

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10 AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly ${\tt IleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer}$ ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe 15 TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlySer ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer HisLysSerProAsnMetValLeuLeuProAlaValAspPheSerLeuGlyGluTrpLys ThrGlnMetGluGluThrLysAlaGlnAspIleLeuGlyAlaValThrLeuLeuGlu GlyValMetAlaAlaArqGlyGlnLeuGlyProThrCysLeuSerSerLeuLeuGlyGln 20 LeuSerGlyGlnValArqLeuLeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnLeu ProProGlnGlyArgThrThrAlaHisLysAspProAsnAlaIlePheLeuSerPheGln HisLeuLeuArgGlyLysValArgPheLeuMetLeuValGlyGlySerThrLeuCysVal ArgGluPheGlyAsnMetAlaSerProAlaProProAlaCysAspLeuArgValLeuSer LysLeuLeuArgAspSerHisValLeuHisSerArgLeuSerGlnCysProGluValHis 25 ProLeuProThrPro (SEQ ID NO:217)

pMON28522

AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro 30 ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly IleGluAlaIleLeuArqAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer 35 ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer HisLysSerProAsnMetAlaValAspPheSerLeuGlyGluTrpLysThrGlnMetGlu GluThrLysAlaGlnAspIleLeuGlyAlaValThrLeuLeuLeuGluGlyValMetAla AlaArgGlyGlnLeuGlyProThrCysLeuSerSerLeuLeuGlyGlnLeuSerGlyGln ValArgLeuLeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnLeuProProGlnGly 40 ArgThrThrAlaHisLysAspProAsnAlaIlePheLeuSerPheGlnHisLeuLeuArg GlyLysValArgPheLeuMetLeuValGlyGlySerThrLeuCysValArgGluPheGly AsnMetAlaSerProAlaProProAlaCysAspLeuArgValLeuSerLysLeuLeuArg AspSerHisValLeuHisSerArgLeuSerGlnCysProGluValHisProLeuProThr ProValLeuLeuPro (SEQ ID NO:218) 45

pMON28523

AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly IleGluAlaIleLeuArqAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer 5 ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer HisLysSerProAsnMetAspPheSerLeuGlyGluTrpLysThrGlnMetGluGluThr LysAlaGlnAspIleLeuGlyAlaValThrLeuLeuLeuGluGlyValMetAlaAlaArg 10 GlyGlnLeuGlyProThrCysLeuSerSerLeuLeuGlyGlnLeuSerGlyGlnValArg LeuLeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnLeuProProGlnGlyArgThr ThrAlaHisLysAspProAsnAlaIlePheLeuSerPheGlnHisLeuLeuArgGlyLys ValArgPheLeuMetLeuValGlyGlySerThrLeuCysValArgGluPheGlyAsnMet AlaSerProAlaProProAlaCysAspLeuArgValLeuSerLysLeuLeuArgAspSer 15 HisValLeuHisSerArgLeuSerGlnCysProGluValHisProLeuProThrProVal LeuLeuProAlaVal (SEQ ID NO:219)

pMON28524

20 AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly IleGluAlaIleLeuArqAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe 25 TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer HisLysSerProAsnMetGlyGluTrpLysThrGlnMetGluGluThrLysAlaGlnAsp IleLeuGlyAlaValThrLeuLeuGluGlyValMetAlaAlaArgGlyGlnLeuGly ProThrCysLeuSerSerLeuLeuGlyGlnLeuSerGlyGlnValArqLeuLeuGly AlaLeuGlnSerLeuLeuGlyThrGlnLeuProProGlnGlyArgThrThrAlaHisLys 30 AspProAsnAlaIlePheLeuSerPheGlnHisLeuLeuArgGlyLysValArgPheLeu MetLeuValGlyGlySerThrLeuCysValArgGluPheGlyAsnMetAlaSerProAla ProProAlaCysAspLeuArgValLeuSerLysLeuLeuArgAspSerHisValLeuHis SerArgLeuSerGlnCysProGluValHisProLeuProThrProValLeuLeuProAla 35 ValAspPheSerLeu (SEQ ID NO:220)

pMON28525

AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro
LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu
ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly
IleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer
ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe
TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer
ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer
HisLysSerProAsnMetGlyProThrCysLeuSerSerLeuLeuGlyGlnLeuSerGly
GlnValArgLeuLeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnLeuProProGln

GlyArgThrThrAlaHisLysAspProAsnAlaIlePheLeuSerPheGlnHisLeuLeu ArgGlyLysValArgPheLeuMetLeuValGlyGlySerThrLeuCysValArgGluPhe GlyAsnMetAlaSerProAlaProProAlaCysAspLeuArgValLeuSerLysLeuLeu ArgAspSerHisValLeuHisSerArgLeuSerGlnCysProGluValHisProLeuPro ThrProValLeuLeuProAlaValAspPheSerLeuGlyGluTrpLysThrGlnMetGlu GluThrLysAlaGlnAspIleLeuGlyAlaValThrLeuLeuGluGlyValMetAla AlaArgGlyGlnLeu (SEQ ID NO:221)

pMON28526

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AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly IleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer 15 ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer HisLysSerProAsnMetGlyThrGlnLeuProProGlnGlyArgThrThrAlaHisLys AspProAsnAlaIlePheLeuSerPheGlnHisLeuLeuArgGlyLysValArgPheLeu 20 MetLeuValGlyGlySerThrLeuCysValArgGluPheGlyAsnMetAlaSerProAla ProProAlaCysAspLeuArgValLeuSerLysLeuLeuArgAspSerHisValLeuHis SerArgLeuSerGlnCysProGluValHisProLeuProThrProValLeuLeuProAla ValAspPheSerLeuGlyGluTrpLysThrGlnMetGluGluThrLysAlaGlnAspIle LeuGlyAlaValThrLeuLeuGluGlyValMetAlaAlaArgGlyGlnLeuGlyPro 25 ThrCysLeuSerSerLeuLeuGlyGlnLeuSerGlyGlnValArgLeuLeuLeuGlyAla LeuGlnSerLeuLeu (SEQ ID NO:222)

pMON28527

35

30 AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly IleGluAlaIleLeuArqAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer HisLysSerProAsnMetGlyArgThrThrAlaHisLysAspProAsnAlaIlePheLeu SerPheGlnHisLeuLeuArgGlyLysValArgPheLeuMetLeuValGlyGlySerThr LeuCysValArgGluPheGlyAsnMetAlaSerProAlaProProAlaCysAspLeuArg 40 ValLeuSerLysLeuLeuArgAspSerHisValLeuHisSerArgLeuSerGlnCysPro GluValHisProLeuProThrProValLeuLeuProAlaValAspPheSerLeuGlyGlu TrpLysThrGlnMetGluGluThrLysAlaGlnAspIleLeuGlyAlaValThrLeuLeu LeuGluGlyValMetAlaAlaArgGlyGlnLeuGlyProThrCysLeuSerSerLeuLeu GlyGlnLeuSerGlyGlnValArgLeuLeuGlyAlaLeuGlnSerLeuLeuGlyThr GlnLeuProProGln (SEQ ID NO:223) 45

pMON28528

AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu ArqLeuProAsnLeuGluSerPheValArqAlaValLysAsnLeuGluAsnAlaSerGly 5 IleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlySer ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer HisLysSerProAsnMetAlaHisLysAspProAsnAlaIlePheLeuSerPheGlnHis 10 LeuLeuArgGlyLysValArgPheLeuMetLeuValGlyGlySerThrLeuCysValArg GluPheGlyAsnMetAlaSerProAlaProProAlaCysAspLeuArqValLeuSerLys LeuLeuArgAspSerHisValLeuHisSerArgLeuSerGlnCysProGluValHisPro LeuProThrProValLeuLeuProAlaValAspPheSerLeuGlyGluTrpLysThrGln MetGluGluThrLysAlaGlnAspIleLeuGlyAlaValThrLeuLeuGluGlyVal 15 MetAlaAlaArgGlyGlnLeuGlyProThrCysLeuSerSerLeuLeuGlyGlnLeuSer GlyGlnValArgLeuLeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnLeuProPro GlnGlyArgThrThr (SEQ ID NO:224)

pMON28529

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AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly IleGluAlaIleLeuArqAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer 25 ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer HisLysSerProAsnMetAspProAsnAlaIlePheLeuSerPheGlnHisLeuLeuArg GlyLysValArgPheLeuMetLeuValGlyGlySerThrLeuCysValArgGluPheGly 30 AsnMetAlaSerProAlaProProAlaCysAspLeuArqValLeuSerLysLeuLeuArq AspSerHisValLeuHisSerArgLeuSerGlnCysProGluValHisProLeuProThr ProValLeuLeuProAlaValAspPheSerLeuGlyGluTrpLysThrGlnMetGluGlu ThrLysAlaGlnAspIleLeuGlyAlaValThrLeuLeuGluGlyValMetAlaAla ArgGlyGlnLeuGlyProThrCysLeuSerSerLeuLeuGlyGlnLeuSerGlyGlnVal 35 ArgLeuLeuLeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnLeuProProGlnGlyArg ThrThrAlaHisLys (SEQ ID NO:225)

pMON28530

40 AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro
LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu
ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly
IleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer
ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe
TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer
ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer
HisLysSerProAsnMetAlaIlePheLeuSerPheGlnHisLeuLeuArgGlyLysVal

ArgPheLeuMetLeuValGlyGlySerThrLeuCysValArgGluPheGlyAsnMetAla SerProAlaProProAlaCysAspLeuArgValLeuSerLysLeuLeuArgAspSerHis ValLeuHisSerArgLeuSerGlnCysProGluValHisProLeuProThrProValLeu LeuProAlaValAspPheSerLeuGlyGluTrpLysThrGlnMetGluGluThrLysAla GlnAspIleLeuGlyAlaValThrLeuLeuLeuGluGlyValMetAlaAlaArgGlyGln LeuGlyProThrCysLeuSerSerLeuLeuGlyGlnLeuSerGlyGlnValArgLeuLeu LeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnLeuProProGlnGlyArgThrThrAla HisLysAspProAsn (SEQ ID NO:226)

10 pMON28533

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AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArqProProAlaPro LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly 15 ${\tt IleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer}$ ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer HisLysSerProAsnMetGluValHisProLeuProThrProValLeuLeuProAlaVal 20 AspPheSerLeuGlyGluTrpLysThrGlnMetGluGluThrLysAlaGlnAspIleLeu GlyAlaValThrLeuLeuGluGlyValMetAlaAlaArqGlyGlnLeuGlyProThr CysLeuSerSerLeuLeuGlyGlnLeuSerGlyGlnValArqLeuLeuGlyAlaLeu GlnSerLeuLeuGlyThrGlnLeuProProGlnGlyArgThrThrAlaHisLysAspPro AsnAlaIlePheLeuSerPheGlnHisLeuLeuArgGlyLysValArgPheLeuMetLeu 25 ValGlyGlySerThrLeuCysValArgGluPheGlyGlyAsnGlyGlyAsnMetAlaSer ProAlaProProAlaCysAspLeuArgValLeuSerLysLeuLeuArgAspSerHisVal LeuHisSerArgLeuSerGlnCysPro (SEQ ID NO:227)

pMON28534

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AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly ${\tt IleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer}$ 35 ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlySer ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer HisLysSerProAsnMetLeuProThrProValLeuLeuProAlaValAspPheSerLeu GlyGluTrpLysThrGlnMetGluGluThrLysAlaGlnAspIleLeuGlyAlaValThr 40 LeuLeuLeuGluGlyValMetAlaAlaArqGlyGlnLeuGlyProThrCysLeuSerSer LeuLeuGlyGlnLeuSerGlyGlnValArqLeuLeuGlyAlaLeuGlnSerLeuLeu GlyThrGlnLeuProProGlnGlyArgThrThrAlaHisLysAspProAsnAlaIlePhe LeuSerPheGlnHisLeuLeuArgGlyLysValArgPheLeuMetLeuValGlyGlySer ThrLeuCysValArgGluPheGlyGlyAsnGlyGlyAsnMetAlaSerProAlaProPro 45 AlaCysAspLeuArgValLeuSerLysLeuLeuArgAspSerHisValLeuHisSerArg LeuSerGlnCysProGluValHisPro (SEQ ID NO:228)

pMON28535

AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArqAsnLeu 5 ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly IleGluAlaIleLeuArqAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlySer ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer 10 HisLysSerProAsnMetValLeuLeuProAlaValAspPheSerLeuGlyGluTrpLys ThrGlnMetGluGluThrLysAlaGlnAspIleLeuGlyAlaValThrLeuLeuLeuGlu GlyValMetAlaAlaArgGlyGlnLeuGlyProThrCysLeuSerSerLeuLeuGlyGln LeuSerGlyGlnValArgLeuLeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnLeu ProProGlnGlyArqThrThrAlaHisLysAspProAsnAlaIlePheLeuSerPheGln 15 HisLeuLeuArgGlyLysValArgPheLeuMetLeuValGlyGlySerThrLeuCysVal ArgGluPheGlyGlyAsnGlyGlyAsnMetAlaSerProAlaProProAlaCysAspLeu ArgValLeuSerLysLeuLeuArgAspSerHisValLeuHisSerArgLeuSerGlnCys ProGluValHisProLeuProThrPro (SEQ ID NO:229)

20 pMON28536

AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArqAsnLeu ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly 25 IleGluAlaIleLeuArqAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer HisLysSerProAsnMetAlaValAspPheSerLeuGlyGluTrpLysThrGlnMetGlu 30 GluThrLysAlaGlnAspIleLeuGlyAlaValThrLeuLeuGluGlyValMetAla AlaArgGlyGlnLeuGlyProThrCysLeuSerSerLeuLeuGlyGlnLeuSerGlyGln ValArqLeuLeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnLeuProProGlnGly ArgThrThrAlaHisLysAspProAsnAlaIlePheLeuSerPheGlnHisLeuLeuArg GlyLysValArgPheLeuMetLeuValGlyGlySerThrLeuCysValArgGluPheGly 35 GlyAsnGlyGlyAsnMetAlaSerProAlaProProAlaCysAspLeuArgValLeuSer LysLeuLeuArgAspSerHisValLeuHisSerArgLeuSerGlnCysProGluValHis ProLeuProThrProValLeuLeuPro (SEQ ID NO:230)

pMON28537

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AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro
LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu
ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly
IleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer
ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe
TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlySer
ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer

HisLysSerProAsnMetAspPheSerLeuGlyGluTrpLysThrGlnMetGluGluThr LysAlaGlnAspIleLeuGlyAlaValThrLeuLeuLeuGluGlyValMetAlaAlaArg GlyGlnLeuGlyProThrCysLeuSerSerLeuLeuGlyGlnLeuSerGlyGlnValArg LeuLeuLeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnLeuProProGlnGlyArgThr ThrAlaHisLysAspProAsnAlaIlePheLeuSerPheGlnHisLeuLeuArgGlyLys ValArgPheLeuMetLeuValGlyGlySerThrLeuCysValArgGluPheGlyGlyAsn GlyGlyAsnMetAlaSerProAlaProProAlaCysAspLeuArgValLeuSerLysLeu LeuArgAspSerHisValLeuHisSerArgLeuSerGlnCysProGluValHisProLeu ProThrProValLeuLeuProAlaVal (SEQ ID NO:231)

10 pMON28538

AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArqProProAlaPro LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu 15 ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly IleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer 20 HisLysSerProAsnMetGlyGluTrpLysThrGlnMetGluGluThrLysAlaGlnAsp IleLeuGlyAlaValThrLeuLeuLeuGluGlyValMetAlaAlaArgGlyGlnLeuGly ProThrCysLeuSerSerLeuLeuGlyGlnLeuSerGlyGlnValArqLeuLeuGly AlaLeuGlnSerLeuLeuGlyThrGlnLeuProProGlnGlyArgThrThrAlaHisLys AspProAsnAlaIlePheLeuSerPheGlnHisLeuLeuArgGlyLysValArgPheLeu 25 MetLeuValGlyGlySerThrLeuCysValArqGluPheGlyGlyAsnGlyGlyAsnMet AlaSerProAlaProProAlaCysAspLeuArgValLeuSerLysLeuLeuArgAspSer HisValLeuHisSerArgLeuSerGlnCysProGluValHisProLeuProThrProVal LeuLeuProAlaValAspPheSerLeu (SEQ ID NO:232)

30 pMON28539

AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArqProProAlaPro LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly 35 IleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer HisLysSerProAsnMetGlyProThrCysLeuSerSerLeuLeuGlyGlnLeuSerGly 40 GlnValArgLeuLeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnLeuProProGln GlyArgThrThrAlaHisLysAspProAsnAlaIlePheLeuSerPheGlnHisLeuLeu ArgGlyLysValArgPheLeuMetLeuValGlyGlySerThrLeuCysValArgGluPhe GlyGlyAsnGlyGlyAsnMetAlaSerProAlaProProAlaCysAspLeuArgValLeu SerLysLeuLeuArgAspSerHisValLeuHisSerArgLeuSerGlnCysProGluVal 45 HisProLeuProThrProValLeuLeuProAlaValAspPheSerLeuGlyGluTrpLys ThrGlnMetGluGluThrLysAlaGlnAspIleLeuGlyAlaValThrLeuLeuLeuGlu GlyValMetAlaAlaArgGlyGlnLeu (SEQ ID NO:233)

pMON28540

AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro 5 ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala ProArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer 10 ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer HisLysSerProAsnMetGlyThrGlnLeuProProGlnGlyArgThrThrAlaHisLys AspProAsnAlaIlePheLeuSerPheGlnHisLeuLeuArgGlyLysValArgPheLeu MetLeuValGlyGlySerThrLeuCysValArqGluPheGlyGlyAsnGlyGlyAsnMet AlaSerProAlaProProAlaCysAspLeuArgValLeuSerLysLeuLeuArgAspSer 15 HisValLeuHisSerArgLeuSerGlnCysProGluValHisProLeuProThrProVal LeuLeuProAlaValAspPheSerLeuGlyGluTrpLysThrGlnMetGluGluThrLys AlaGlnAspIleLeuGlyAlaValThrLeuLeuGluGlyValMetAlaAlaArqGly GlnLeuGlyProThrCysLeuSerSerLeuLeuGlyGlnLeuSerGlyGlnValArgLeu LeuLeuGlyAlaLeuGlnSerLeuLeu (SEQ ID NO:234)

pMON28541

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AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArqProProAlaPro LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArqAsnLeu 25 ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly ${\tt IleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer}$ ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer 30 HisLysSerProAsnMetGlyArgThrThrAlaHisLysAspProAsnAlaIlePheLeu SerPheGlnHisLeuLeuArgGlyLysValArgPheLeuMetLeuValGlyGlySerThr LeuCysValArqGluPheGlyGlyAsnGlyGlyAsnMetAlaSerProAlaProProAla CysAspLeuArgValLeuSerLysLeuLeuArgAspSerHisValLeuHisSerArgLeu SerGlnCysProGluValHisProLeuProThrProValLeuLeuProAlaValAspPhe 35 SerLeuGlyGluTrpLysThrGlnMetGluGluThrLysAlaGlnAspIleLeuGlyAla ValThrLeuLeuGluGlyValMetAlaAlaArqGlyGlnLeuGlyProThrCysLeu SerSerLeuLeuGlyGlnLeuSerGlyGlnValArgLeuLeuLeuGlyAlaLeuGlnSer LeuLeuGlyThrGlnLeuProProGln (SEQ ID NO:235)

40 pMON28542

AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro
LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu
ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly
IleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer
ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe
TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGer

ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer HisLysSerProAsnMetAlaHisLysAspProAsnAlaIlePheLeuSerPheGlnHis LeuLeuArgGlyLysValArgPheLeuMetLeuValGlyGlySerThrLeuCysValArg GluPheGlyGlyAsnGlyGlyAsnMetAlaSerProAlaProProAlaCysAspLeuArg ValLeuSerLysLeuLeuArgAspSerHisValLeuHisSerArgLeuSerGlnCysPro GluValHisProLeuProThrProValLeuLeuProAlaValAspPheSerLeuGlyGlu TrpLysThrGlnMetGluGluThrLysAlaGlnAspIleLeuGlyAlaValThrLeuLeu LeuGluGlyValMetAlaAlaArgGlyGlnLeuGlyProThrCysLeuSerSerLeuLeu GlyGlnLeuSerGlyGlnValArgLeuLeuLeuGlyAlaLeuGlnSerLeuLeuGlyThr GlnLeuProProGlnGlyArgThrThr (SEQ ID NO:236)

pMON28543

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AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro 15 LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly IleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer 20 ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer HisLysSerProAsnMetAspProAsnAlaIlePheLeuSerPheGlnHisLeuLeuArg GlyLysValArgPheLeuMetLeuValGlyGlySerThrLeuCysValArgGluPheGly GlyAsnGlyGlyAsnMetAlaSerProAlaProProAlaCysAspLeuArgValLeuSer LysLeuLeuArgAspSerHisValLeuHisSerArgLeuSerGlnCysProGluValHis 25 ProLeuProThrProValLeuLeuProAlaValAspPheSerLeuGlyGluTrpLysThr GlnMetGluGluThrLysAlaGlnAspIleLeuGlyAlaValThrLeuLeuLeuGluGly ValMetAlaAlaArgGlyGlnLeuGlyProThrCysLeuSerSerLeuLeuGlyGlnLeu SerGlyGlnValArgLeuLeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnLeuPro ProGlnGlyArgThrThrAlaHisLys (SEQ ID NO:237)

pMON28544

AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArgAsnLeu 35 ArgLeuProAsnLeuGluSerPheValArgAlaValLysAsnLeuGluAsnAlaSerGly ${\tt IleGluAlaIleLeuArgAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer}$ ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer 40 HisLysSerProAsnMetAlaIlePheLeuSerPheGlnHisLeuLeuArgGlyLysVal ArgPheLeuMetLeuValGlyGlySerThrLeuCysValArgGluPheGlyGlyAsnGly GlyAsnMetAlaSerProAlaProProAlaCysAspLeuArgValLeuSerLysLeuLeu ArgAspSerHisValLeuHisSerArgLeuSerGlnCysProGluValHisProLeuPro ThrProValLeuLeuProAlaValAspPheSerLeuGlyGluTrpLysThrGlnMetGlu 45 GluThrLysAlaGlnAspIleLeuGlyAlaValThrLeuLeuGluGlyValMetAla AlaArgGlyGlnLeuGlyProThrCysLeuSerSerLeuLeuGlyGlnLeuSerGlyGln ValArgLeuLeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnLeuProProGlnGly ArgThrThrAlaHisLysAspProAsn (SEQ ID NO:238)

pMON28545

AlaAsnCysSerIleMetIleAspGluIleIleHisHisLeuLysArgProProAlaPro LeuLeuAspProAsnAsnLeuAsnAspGluAspValSerIleLeuMetAspArqAsnLeu ArqLeuProAsnLeuGluSerPheValArqAlaValLysAsnLeuGluAsnAlaSerGly IleGluAlaIleLeuArqAsnLeuGlnProCysLeuProSerAlaThrAlaAlaProSer ArgHisProIleIleIleLysAlaGlyAspTrpGlnGluPheArgGluLysLeuThrPhe 10 TyrLeuValThrLeuGluGlnAlaGlnGluGlnGlnTyrValGluGlyGlyGlyGlySer ProGlyGluProSerGlyProIleSerThrIleAsnProSerProProSerLysGluSer HisLysSerProAsnMetAspProAsnAlaIlePheLeuSerPheGlnHisLeuLeuArg GlyLysValArgPheLeuMetLeuValGlyGlySerThrLeuCysValArgGluPheGly GlyAsnMetAlaSerProAlaProProAlaCysAspLeuArgValLeuSerLysLeuLeu 15 ArgAspSerHisValLeuHisSerArgLeuSerGlnCysProGluValHisProLeuPro ThrProValLeuLeuProAlaValAspPheSerLeuGlyGluTrpLysThrGlnMetGlu GluThrLysAlaGlnAspIleLeuGlyAlaValThrLeuLeuGluGlyValMetAla AlaArgGlyGlnLeuGlyProThrCysLeuSerSerLeuLeuGlyGlnLeuSerGlyGln ValArqLeuLeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnGlyArgThrThrAla 20 HisLys (SEQ ID NO:239)

pMON32132

25 SerProAlaProProAlaCysAspLeuArgValLeuSerLysLeuLeuArgAspSerHis ValLeuHisSerArgLeuSerGlnCysProGluValHisProLeuProThrProValLeu LeuProAlaValAspPheSerLeuGlyGluTrpLysThrGlnMetGluGluThrLysAla GlnAspIleLeuGlyAlaValThrLeuLeuLeuGluGlyValMetAlaAlaArgGlyGln LeuGlyProThrCysLeuSerSerLeuLeuGlyGlnLeuSerGlyGlnValArgLeuLeu LeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnLeuProProGlnGlyArgThrThrAla HisLysAspProAsnAlaIlePheLeuSerPheGlnHisLeuLeuArgGlyLysValArg PheLeuMetLeuValGlyGlySerThrLeuCysValArg (SEQ ID NO:252)

35 PMON32133

SerProAlaProProAlaCysAspLeuArgValLeuSerLysLeuLeuArgAspSerHis ValLeuHisSerArgLeuSerGlnCysProGluValHisProLeuProThrProValLeu LeuProAlaValAspPheSerLeuGlyGluTrpLysThrGlnMetGluGluThrLysAla GlnAspIleLeuGlyAlaValThrLeuLeuLeuGluGlyValMetAlaAlaArgGlyGln LeuGlyProThrCysLeuSerSerLeuLeuGlyGlnLeuSerGlyGlnValArgLeuLeu LeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnGlyArgThrThrAlaHisLysAspPro AsnAlaIlePheLeuSerPheGlnHisLeuLeuArgGlyLysValArgPheLeuMetLeu ValGlyGlySerThrLeuCysValArg (SEQ ID NO:253)

PMON32134

45

SerProAlaProProAlaCysAspLeuArgValLeuSerLysLeuLeuArgAspSerHis ValLeuHisSerArgLeuSerGlnCysProGluValHisProLeuProThrProValLeu LeuProAlaValAspPheSerLeuGlyGluTrpLysThrGlnMetGluGluThrLysAla GlnAspIleLeuGlyAlaValThrLeuLeuLeuGluGlyValMetAlaAlaArgGlyGln LeuGlyProThrCysLeuSerSerLeuLeuGlyGlnLeuSerGlyGlnValArgLeuLeu LeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnLeuProProGlnGlyArgThrThrAla HisLysAspProAsnAlaIlePheLeuSerPheGlnHisLeuLeuArgGlyLysValArg PheLeuMetLeuValGlyGlySerThrLeuCysValArg (SEQ ID NO:254)

pmon16017.pep

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Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu 15 Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn 16 Asp 31 Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn 46 Leu Glu Ser Phe Val Arq Ala Val Lys Asn Leu Glu Asn Ala 20 Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro 61 Ser 76 Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Lys Ala Gly 25 91 Asp Trp Gln Glu Phe Arq Glu Lys Leu Thr Phe Tyr Leu Val Thr 106 Leu Glu Gln Ala Gln Glu Gln Tyr Val Glu Gly Gly Gly Gly 121 Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro 30 Ser 136 Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu 151 Glu 35 166 Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys 181 Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu 196 Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser 40 Cys 211 Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His 226 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly 45 241 Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp

- 256 Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu
 271 Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala
 5 286 Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala
 301 Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg
 316 His Leu Ala Gln Pro Asp Met Ala Thr Pro (SEQ ID NO:271)
 - pmon16018.pep
- Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His 15 Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn 16 Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro 31 Asn 20 46 Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser 61 Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Lys Ala 76 25 Gly 31 Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr 106 Leu Glu Gln Ala Gln Glu Gln Tyr Val Glu Gly Gly Gly 30 121 Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser 136 Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Leu Gly 151 Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu 35 Glu 176 Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys 191 Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu 40 206 Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys 221 Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His 236 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu 45 Gly 251 Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp

- 266 Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu
 281 Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala
 296 Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala
 311 Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg
- 326 His Leu Ala Gln Pro Asp Met Ala Thr Pro (SEQ ID NO:272)

pmon16019.pep

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Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His 15 Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn 16 Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro 31 Asn 20 46 Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro 61 Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Lys Ala 76 25 Gly 91 Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Tyr Val Glu Gly Gly 106 Gly 30 121 Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser 136 Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly 151 35 Ala 166 Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 181 Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 40 196 Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys 211 Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu 226 Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu 45 Asp 241 Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln

256 Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln 271 Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly 5 286 Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser 301 Tyr Arg Val Leu Arg His Leu Ala Gln Pro Asp Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser (SEQ ID NO:273) 316 10

pmon16020.pep

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His 15 Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn 16 Asp 31 Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn 20 Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala 46 Ser 61 Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser 76 Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Lys Ala 25 Gly 91 Asp Trp Gln Glu Phe Arq Glu Lys Leu Thr Phe Tyr Leu Val Thr 106 Leu Glu Gln Ala Gln Glu Gln Tyr Val Glu Gly Gly Gly 30 121 Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser 136 Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Glu Gln 151 Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys 35 Leu 166 Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys 181 Pro 40 196 Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser 211 Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp 226 45 Val 241 Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly

256 Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe
271 Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser
286 His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His
301 Leu Ala Gln Pro Asp Met Ala Thr Pro Leu Gly Pro Ala Ser Ser
316 Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu (SEQ ID NO:274)

pmon16021.pep

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Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His 15 Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn 16 Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro 31 Asn 20 46 Leu Glu Ser Phe Val Arq Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro 61 Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Lys Ala 76 25 Gly 91 Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Tyr Val Glu Gly Gly 106 Gly 30 121 Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser 136 Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys 151 35 Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His 166 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly 181 Ile 40 196 Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val 211 Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly 226 Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 45 Phe 241 Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser

256 His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His 271 Leu Ala Gln Pro Asp Met Ala Thr Pro Leu Gly Pro Ala Ser Ser 5 Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg 286 Lys 301 Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val (SEQ ID NO:275) 316 10

pmon16022.pep

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His 15 Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn 16 Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro 31 Asn 20 46 Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser 61 Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser 76 Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Lys Ala 25 Gly 91 Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Tyr Val Glu Gly Gly 106 Gly 30 121 Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser 136 Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Pro Leu 151 Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 35 Ser 166 Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 181 Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu 40 196 Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met 211 Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala 226 Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly 45 Val 241 Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg

256 Val Leu Arq His Leu Ala Gln Pro Asp Met Ala Thr Pro Leu Gly 271 Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu 5 286 Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys 301 Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu 316 Leu Gly His Ser Leu Gly Ile Pro Trp Ala (SEQ ID NO:276) 10

pmon16023.pep

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His 15 Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn 16 Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro 31 Asn 20 46 Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser 61 Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser 76 Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Lys Ala 25 Gly 91 Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr 106 Leu Glu Gln Ala Gln Glu Gln Tyr Val Glu Gly Gly Gly Gly 30 121 Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser 136 Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Gln Ala 151 Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu 35 Phe 166 Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu 181 Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 40 196 Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro 211 Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala 226 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu 45 Gln 241 Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln

256 Pro Asp Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln 271 Gly 5 286 Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu 301 Cys His Pro Glu Glu Leu Val Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser (SEQ ID NO:277) 316 10

pmon16024.pep

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His 15 Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn 16 Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro 31 Asn 20 46 Leu Glu Ser Phe Val Arq Ala Val Lys Asn Leu Glu Asn Ala Ser 61 Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser 76 Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Lys Ala 25 Gly 91 Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr 106 Leu Glu Gln Ala Gln Glu Gln Tyr Val Glu Gly Gly Gly 30 121 Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser 136 Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Leu Gln 151 Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu 35 Tyr 166 Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly 181 Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr 40 196 Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu 211 Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln 226 Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser 45 Phe 241 Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Asp

Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser 256 Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp 271 Gly 5 286 Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His 301 Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp 316 Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala (SEQ ID NO:278) 10

pmon16025.pep

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His 15 Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn 16 Asp 31 Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn 20 46 Leu Glu Ser Phe Val Arq Ala Val Lys Asn Leu Glu Asn Ala Ser 61 Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser 76 Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Lys Ala 25 Gly 91 Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr 106 Leu Glu Gln Ala Gln Glu Gln Tyr Val Glu Gly Gly Gly 30 121 Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser 136 Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Leu Ala 151 Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln 35 Gly 166 Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr 181 Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile 40 196 Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg 211 Arg 226 Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu 45 Glu 241 Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Asp Met Ala

Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu 256 Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala 271 Ala 5 Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 286 Glu 301 Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 316 Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln (SEQ ID NO:279) 10

pmon16026.pep

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His 1 15 Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn 16 Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro 31 Asn 20 Leu Glu Ser Phe Val Arq Ala Val Lys Asn Leu Glu Asn Ala 46 Ser 61 Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser 76 Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Lys Ala 25 Gly 91 Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr 106 Leu Glu Gln Ala Gln Glu Gln Tyr Val Glu Gly Gly Gly Gly 30 121 Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser 136 Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro 151 35 Ala 166 Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu 181 Arq 40 196 His Leu Ala Gln Pro Asp Met Ala Thr Pro Leu Gly Pro Ala Ser 211 Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg 226 Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys 45 Ala 241 Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His

Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser 256 Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly 271 Leu 5 286 Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro 301 Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp 316 Phe Ala Thr Thr Ile Trp Gln Gln Met Glu (SEQ ID NO:280) 10

pmon16027.pep

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His 15 Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn 16 Asp 31 Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn 20 46 Leu Glu Ser Phe Val Arq Ala Val Lys Asn Leu Glu Asn Ala Ser 61 Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser 76 Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Lys Ala 25 Gly 91 Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr 106 Leu Glu Gln Ala Gln Glu Gln Gln Tyr Val Glu Gly Gly Gly 30 121 Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser 136 Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Gly Met 151 Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 35 Ala 166 Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 181 Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 40 196 Ala Gln Pro Asp Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu 211 Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile 226 Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr 45 Tyr 241 Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu

Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala 256 Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe 271 Leu 5 286 Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu 301 Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala 316 Thr Thr Ile Trp Gln Gln Met Glu Glu Leu (SEQ ID NO:281) 10

pmon16028.pep

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His 15 Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn 16 Asp 31 Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn 20 Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala 46 Ser 61 Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser 76 Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Lys Ala 25 Gly 91 Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr 106 Leu Glu Gln Ala Gln Glu Gln Tyr Val Glu Gly Gly Gly 30 121 Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser 136 Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Ser Phe 151 Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 35 Asp Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser 166 Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp 181 Gly 40 196 Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His 211 Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp 226 Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala 45 Gly 241 Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu

- 256 Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu 271 Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp 5 286 Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr 301 Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala 316 Gly Gly Val Leu Val Ala Ser His Leu Gln (SEQ ID NO:282) 10
- MetAlaGlyArgThrThrAlaHisLysAspProAsnAlaIlePheLeuSerPheGlnHis LeuLeuArgGlyLysValArgPheLeuMetLeuValGlyGlySerThrLeuAlaValArg GluPheGlyGlyAsnMetAlaSerProAlaProProAlaAlaAspLeuArgValLeuSer LysLeuLeuArgAspSerHisValLeuHisSerArgLeuSerGlnCysProGluValHis ProLeuProThrProValLeuLeuProAlaValAspPheSerLeuGlyGluTrpLysThr GlnMetGluGluThrLysAlaGlnAspIleLeuGlyAlaValThrLeuLeuLeuGluGly ValMetAlaAlaArgGlyGlnLeuGlyProThrCysLeuSerSerLeuLeuGlyGlnLeu SerGlyGlnValArgLeuLeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnLeuPro ProGln (SEQ ID NO:284);
- MetAlaGlyProThrCysLeuSerSerLeuLeuGlyGlnLeuSerGlyGlnValArgLeu
 LeuLeuGlyAlaLeuGlnSerLeuLeuGlyThrGlnLeuProProGlnGlyArgThrThr
 AlaHisLysAspProAsnAlaIlePheLeuSerPheGlnHisLeuLeuArgGlyLysVal
 ArgPheLeuMetLeuValGlyGlySerThrLeuAlaValArgGluPheGlyGlyAsnMet
 AlaSerProAlaProProAlaAlaAspLeuArgValLeuSerLysLeuLeuArgAspSer
 HisValLeuHisSerArgLeuSerGlnCysProGluValHisProLeuProThrProVal
 LeuLeuProAlaValAspPheSerLeuGlyGluTrpLysThrGlnMetGluGluThrLys
 AlaGlnAspIleLeuGlyAlaValThrLeuLeuLeuGluGlyValMetAlaAlaArgGly
 GlnLeu (SEQ ID NO:285)